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=> d his


     (FILE 'HOME' ENTERED AT 14:09:50 ON 19 DEC 2000)
               SET COST OFF

     FILE 'REGISTRY' ENTERED AT 14:09:57 ON 19 DEC 2000
               E CALCINEURIN/CN
L1               1 S E3
L2             109 S CALCINEURIN NOT L1

     FILE 'HCAPLUS' ENTERED AT 14:10:54 ON 19 DEC 2000
L3            6018 S L1
L4              55 S L2
L5            1876 S CALCINEURIN?
L6            6737 S L3-L5
               E ARMISTEAD D/AU
L7              36 S E3,E5-E7
               E FITZGIBBON M/AU
L8              17 S E3-E8
               E FLEMING M/AU
L9              30 S E3,E4,E26-E28
               E GRIFFITH J/AU
L10             57 S E3,E18,E29,E37
L11              1 S E57
               E KIM E/AU
L12             80 S E3,E8
               E KIM EUNICE/AU
L13             19 S E4-E6
               E KIM J/AU
L14            479 S E3,E25
               E KIM JOE/AU
L15              3 S E3
               E KIM JOSEPH/AU
L16             18 S E3,E8,E9
               E SINTCHAK M/AU
L17             11 S E4,E5
               E THOMSON J/AU
L18            244 S E3-E8
               E THOMSON JOHN/AU
L19             99 S E3-E5
               E WILSON K/AU
L20             97 S E3,E20
               E WILSON KEITH/AU
L21            108 S E3,E14-E16
L22              6 S L6 AND L7-L21

     FILE 'REGISTRY' ENTERED AT 14:17:54 ON 19 DEC 2000
L23              1 S 104987-11-3
L24             17 S C44H69NO12/MF AND 46.150.1/RID AND 4/NR
L25             12 S L24 AND 15 19
L26              9 S L25 AND 1 7 20 21
L27              9 S L26 AND 14 16
L28              9 S L27 AND 4 10 12 18
L29              8 S L28 NOT L23
L30              4 S L29 NOT (14C# OR 13C# OR LABELED)
L31              3 S L30 NOT 137635-83-7
L32              4 S L23,L31
               SEL RN
L33              9 S E1-E4/CRN

     FILE 'HCAPLUS' ENTERED AT 14:26:45 ON 19 DEC 2000
L34           2860 S L23
L35             11 S L33
L36           4261 S FK506 OR FK 506 OR TACROLIMUS OR TSUKUBAENOLIDE OR PROGRAF OR
L37            577 S L6 AND L34-L36
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L38          613 S FKBP12 OR FKBP 12 OR FK()(BP12 OR BP 12)
L39          151 S L6 AND L38
L40           32 S L6 AND (CNA OR CNB)
L41           91 S L6 AND ?CRYS?
L42           21 S L41 AND L37-L40
L43          188 S L6 AND CONFORMATION
L44           43 S L6 AND X RAY
L45           51 S L41 AND L43,L44
L46           17 S L42 AND L45
L47           28 S L6 AND (3D OR THREE DIMENSION?)
L48            8 S L47 AND L37-L40
L49           25 S L42,L46,L48
L50            6 S L22 AND L37,L39-L49
L51          150 S L6 AND MOLECULAR (S) STRUCTURE
L52            4 S L50 AND L51
L53            6 S L50,L52
L54          354 S L41,L43,L47,L51
L55           31 S L44 AND L54
                 E COMPUTER GRAPHIC/CT
                 E E4+ALL/CT
L56            1 S E1,E2 AND L6
                 E COMPUTER PROGRAM/CT
                 E E3+ALL/CT
L57            5 S E1,E2,E10 AND L6
                 E COMPUTER APPLICATION/CT
L58           25 S E3+ALL/CT AND L6
                 E COMPUTER/CT
                 E E3+ALL/CT
L59            9 S E2+ALL/CT AND L6
                 E CRYSTAL/CT
L60           86 S E181+ALL/CT AND L6
L61            0 S E189+ALL/CT AND L6
L62           30 S E194+ALL/CT AND L6
L63           30 S E207+ALL/CT AND L6
L64           25 S L56-L59
L65          138 S L60,L62,L63,L41
L66          120 S L3 AND L65
L67           16 S L66 AND L34-L40
L68          141 S L54 AND L56-L65
L69           24 S L6 AND MOLECULAR MODEL?
L70           28 S L68 AND X RAY
L71          136 S L68 AND L65
L72           25 S L56-L59
L73           71 S L22,L49,L50,L55,L64,L67,L69,L70,L72
L74           22 S CRYST?/SC,SX AND L6
L75           83 S L74,L73
L76           67 S L3,L4 AND L75
L77           20 S L34,L35 AND L76
L78           67 S L76,L77
L79           16 S L75 NOT L78
L80            1 S L79 AND COMPUTER/TI
L81           65 S L78 AND (MOLECULAR (S) MODEL? OR X RAY OR CONFORM? OR STRUCTU
L82           66 S L80,L81
L83           68 S L53,L82
L84            9 S L47 AND L83
L85           68 S L83,L84
L86           29 S L85 AND 7/SC
L87           68 S L85,L86
                 E OPTICAL/CT
                 E OPTICAL IMAG/CT
L88            2 S E6+NT/CT AND L6
                 E OPTICAL MEMORY/CT
L89            1 S E5+ALL/CT AND L6
                 E X RAY/CT
                 E X-RAY/CT
L90           10 S E3+ALL/CT AND L6
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L91             8 S L88-L90 AND L41-L87
L92             1 S L91 AND 9/SC
L93             2 S L91 AND 9/SX
L94            68 S L87,L92,L93
                  SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 15:02:39 ON 19 DEC 2000
L95             2 S E1-E3

=> fil reg

FILE 'REGISTRY' ENTERED AT 15:02:54 ON 19 DEC 2000
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STRUCTURE FILE UPDATES:   18 DEC 2000  HIGHEST RN 309710-54-1
DICTIONARY FILE UPDATES:  18 DEC 2000  HIGHEST RN 309710-54-1

TSCA INFORMATION NOW CURRENT THROUGH July 8, 2000

  Please note that search-term pricing does apply when
  conducting SmartSELECT searches.

Structure search limits have been increased.  See HELP SLIMIT
for details.

=> d ide can tot


L95  ANSWER 1 OF 2  REGISTRY  COPYRIGHT 2000 ACS
RN   104987-11-3  REGISTRY
CN   15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-
     tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-
     dihydroxy-3-[(1E)-2-[(1R,3R,4R)-4-hydroxy-3-methoxycyclohexyl]-1-
     methylethenyl]-14,16-dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-,
     (3S,4R,5S,8R,9E,12S,14S,15R,16S,18R,19R,26aS)- (9CI)  (CA INDEX NAME)
OTHER CA INDEX NAMES:
CN   15,19-Epoxy-3H-pyrido[2,1-c][1,4]oxaazacyclotricosine-1,7,20,21(4H,23H)-
     tetrone, 5,6,8,11,12,13,14,15,16,17,18,19,24,25,26,26a-hexadecahydro-5,19-
     dihydroxy-3-[2-(4-hydroxy-3-methoxycyclohexyl)-1-methylethenyl]-14,16-
     dimethoxy-4,10,12,18-tetramethyl-8-(2-propenyl)-, [3S-
     [3R*[E(1S*,3S*,4S*)],4S*,5R*,8S*,9E,12R*,14R*,15S*,16R*,18S*,19S*,26aR*]]-
OTHER NAMES:
CN   (-)-FK 506
CN   FK 506
CN   FR 900506
CN   Fujimycin
CN   L 679934
CN   Prograf
CN   Tacrolimus
CN   Tsukubaenolide
FS   STEREOSEARCH
MF   C44 H69 N O12
CI   COM
SR   CA
LC   STN Files:   ADISINSIGHT, AGRICOLA, ANABSTR, BEILSTEIN*, BIOBUSINESS,
       BIOSIS, BIOTECHNO, CA, CAPLUS, CASREACT, CBNB, CEN, CHEMCATS, CIN,
       CSCHEM, DDFU, DIOGENES, DRUGNL, DRUGPAT, DRUGU, DRUGUPDATES, EMBASE,
       IFICDB, IFIUDB, IMSDIRECTORY, MEDLINE, MRCK*, PHAR, PROMT, RTECS*,
       SYNTHLINE, TOXLINE, TOXLIT, USAN, USPATFULL
         (*File contains numerically searchable property data)
     Other Sources:   WHO

Absolute stereochemistry.
Double bond geometry as shown.
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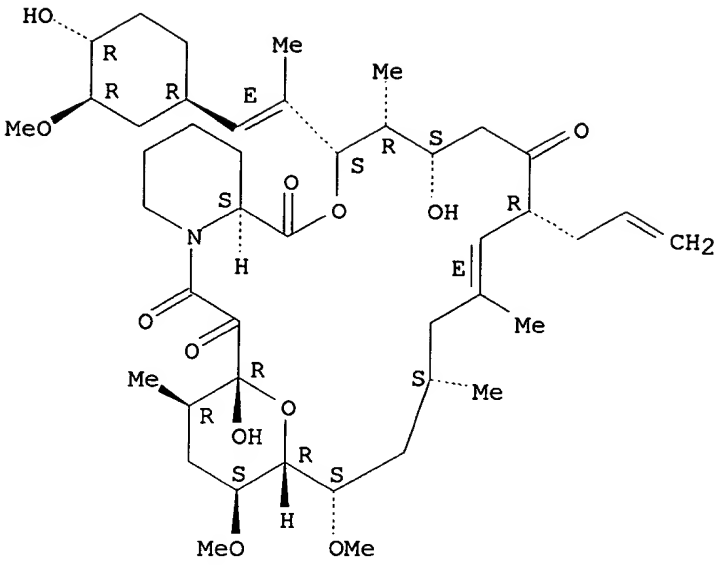

2850 REFERENCES IN FILE CA (1967 TO DATE)
107 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
2860 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:359000

REFERENCE 2: 133:358995

REFERENCE 3: 133:355211

REFERENCE 4: 133:355075

REFERENCE 5: 133:344344

REFERENCE 6: 133:344157

REFERENCE 7: 133:344058

REFERENCE 8: 133:340119

REFERENCE 9: 133:340104

REFERENCE 10: 133:329582

L95 ANSWER 2 OF 2 REGISTRY COPYRIGHT 2000 ACS
RN **9025-75-6** REGISTRY
CN Phosphatase, phosphoprotein (9CI) (CA INDEX NAME)
OTHER NAMES:
CN Calcineurin
CN Calcineurin phosphatase
CN Calponin phosphatase
CN Casein phosphatase
CN E.C. 3.1.3.16
CN Phosphoprotein phosphatase
CN Phosphoprotein phosphohydrolase
CN Phosphoserine/phosphothreonine protein phosphatase
CN Phosphoseryl protein phosphatase
CN Phosphospectrin phosphatase
CN Phosphothreonine phosphatase
CN Phosphothreonyl protein phosphatase
CN Protein D phosphatase
CN Protein phosphatase
CN Protein phosphatase 2C.alpha.

CN Protein-serine/threonine phosphatase
CN Proteins (specific proteins and subclasses), calcineurins
CN Proteins, calcineurins
CN Proteins, CaM-BP80
CN Serine-threonine protein phosphatase
CN Serine/threonine phosphatase
CN Serine/threonine phosphoprotein phosphatase
CN Serine/threonine-specific protein phosphatase
DR **137951-12-3, 143670-43-3**
MF Unspecified
CI MAN
LC STN Files: AGRICOLA, ANABSTR, BIOBUSINESS, BIOSIS, BIOTECHNO, CA, CAPLUS, CEN, CHEMCATS, CIN, EMBASE, PROMT, TOXLIT, USPATFULL

*** STRUCTURE DIAGRAM IS NOT AVAILABLE ***
5948 REFERENCES IN FILE CA (1967 TO DATE)
44 REFERENCES TO NON-SPECIFIC DERIVATIVES IN FILE CA
5972 REFERENCES IN FILE CAPLUS (1967 TO DATE)

REFERENCE 1: 133:361886

REFERENCE 2: 133:361600

REFERENCE 3: 133:361486

REFERENCE 4: 133:361393

REFERENCE 5: 133:361175

REFERENCE 6: 133:360378

REFERENCE 7: 133:360337

REFERENCE 8: 133:359799

REFERENCE 9: 133:359270

REFERENCE 10: 133:355075

=> fil hcaplus

FILE 'HCAPLUS' ENTERED AT 15:03:06 ON 19 DEC 2000
USE IS SUBJECT TO THE TERMS OF YOUR STN CUSTOMER AGREEMENT.
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FILE COVERS 1967 - 19 Dec 2000 VOL 133 ISS 26
FILE LAST UPDATED: 18 Dec 2000 (20001218/ED)

This file contains CAS Registry Numbers for easy and accurate substance identification.

This file supports REG1stRY for direct browsing and searching of all substance data from the REGISTRY file. Enter HELP FIRST for more information.

Now you can extend your author, patent assignee, patent information, and title searches back to 1907. The records from 1907-1966 now have this searchable data in CAOLD. You now have electronic access to all

of CA: 1907 to 1966 in CAOLD and 1967 to the present in HCAPLUS on STN.

=> dh is

DH IS NOT A RECOGNIZED COMMAND
The previous command name entered was not recognized by the system.
For a list of commands available to you in the current file, enter
"HELP COMMANDS" at an arrow prompt (=>).

=> d his

(FILE 'HOME' ENTERED AT 14:09:50 ON 19 DEC 2000)
SET COST OFF

FILE 'REGISTRY' ENTERED AT 14:09:57 ON 19 DEC 2000
E CALCINEURIN/CN
L1 1 S E3
L2 109 S CALCINEURIN NOT L1

FILE 'HCAPLUS' ENTERED AT 14:10:54 ON 19 DEC 2000
L3 6018 S L1
L4 55 S L2
L5 1876 S CALCINEURIN?
L6 6737 S L3-L5
E ARMISTEAD D/AU
L7 36 S E3,E5-E7
E FITZGIBBON M/AU
L8 17 S E3-E8
E FLEMING M/AU
L9 30 S E3,E4,E26-E28
E GRIFFITH J/AU
L10 57 S E3,E18,E29,E37
L11 1 S E57
E KIM E/AU
L12 80 S E3,E8
E KIM EUNICE/AU
L13 19 S E4-E6
E KIM J/AU
L14 479 S E3,E25
E KIM JOE/AU
L15 3 S E3
E KIM JOSEPH/AU
L16 18 S E3,E8,E9
E SINTCHAK M/AU
L17 11 S E4,E5
E THOMSON J/AU
L18 244 S E3-E8
E THOMSON JOHN/AU
L19 99 S E3-E5
E WILSON K/AU
L20 97 S E3,E20
E WILSON KEITH/AU
L21 108 S E3,E14-E16
L22 6 S L6 AND L7-L21

FILE 'REGISTRY' ENTERED AT 14:17:54 ON 19 DEC 2000
L23 1 S 104987-11-3
L24 17 S C44H69NO12/MF AND 46.150.1/RID AND 4/NR
L25 12 S L24 AND 15 19
L26 9 S L25 AND 1 7 20 21
L27 9 S L26 AND 14 16
L28 9 S L27 AND 4 10 12 18
L29 8 S L28 NOT L23
L30 4 S L29 NOT (14C# OR 13C# OR LABELED)

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L31           3 S L30 NOT 137635-83-7
L32           4 S L23,L31
                SEL RN
L33           9 S E1-E4/CRN

     FILE 'HCAPLUS' ENTERED AT 14:26:45 ON 19 DEC 2000
L34        2860 S L23
L35          11 S L33
L36        4261 S FK506 OR FK 506 OR TACROLIMUS OR TSUKUBAENOLIDE OR PROGRAF OR
L37         577 S L6 AND L34-L36
L38         613 S FKBP12 OR FKBP 12 OR FK()(BP12 OR BP 12)
L39         151 S L6 AND L38
L40          32 S L6 AND (CNA OR CNB)
L41          91 S L6 AND ?CRYS?
L42          21 S L41 AND L37-L40
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L44          43 S L6 AND X RAY
L45          51 S L41 AND L43,L44
L46          17 S L42 AND L45
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L48           8 S L47 AND L37-L40
L49          25 S L42,L46,L48
L50           6 S L22 AND L37,L39-L49
L51         150 S L6 AND MOLECULAR (S) STRUCTURE
L52           4 S L50 AND L51
L53           6 S L50,L52
L54         354 S L41,L43,L47,L51
L55          31 S L44 AND L54
                E COMPUTER GRAPHIC/CT
                E E4+ALL/CT
L56           1 S E1,E2 AND L6
                E COMPUTER PROGRAM/CT
                E E3+ALL/CT
L57           5 S E1,E2,E10 AND L6
                E COMPUTER APPLICATION/CT
L58          25 S E3+ALL/CT AND L6
                E COMPUTER/CT
                E E3+ALL/CT
L59           9 S E2+ALL/CT AND L6
                E CRYSTAL/CT
L60          86 S E181+ALL/CT AND L6
L61           0 S E189+ALL/CT AND L6
L62          30 S E194+ALL/CT AND L6
L63          30 S E207+ALL/CT AND L6
L64          25 S L56-L59
L65         138 S L60,L62,L63,L41
L66         120 S L3 AND L65
L67          16 S L66 AND L34-L40
L68         141 S L54 AND L56-L65
L69          24 S L6 AND MOLECULAR MODEL?
L70          28 S L68 AND X RAY
L71         136 S L68 AND L65
L72          25 S L56-L59
L73          71 S L22,L49,L50,L55,L64,L67,L69,L70,L72
L74          22 S CRYST?/SC,SX AND L6
L75          83 S L74,L73
L76          67 S L3,L4 AND L75
L77          20 S L34,L35 AND L76
L78          67 S L76,L77
L79          16 S L75 NOT L78
L80           1 S L79 AND COMPUTER/TI
L81          65 S L78 AND (MOLECULAR (S) MODEL? OR X RAY OR CONFORM? OR STRUCTU
L82          66 S L80,L81
L83          68 S L53,L82
L84           9 S L47 AND L83
L85          68 S L83,L84
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L86          29 S L85 AND 7/SC
L87          68 S L85,L86
                E OPTICAL/CT
                E OPTICAL IMAG/CT
L88           2 S E6+NT/CT AND L6
                E OPTICAL MEMORY/CT
L89           1 S E5+ALL/CT AND L6
                E X RAY/CT
                E X-RAY/CT
L90          10 S E3+ALL/CT AND L6
L91           8 S L88-L90 AND L41-L87
L92           1 S L91 AND 9/SC
L93           2 S L91 AND 9/SX
L94          68 S L87,L92,L93
                SEL HIT RN

     FILE 'REGISTRY' ENTERED AT 15:02:39 ON 19 DEC 2000
L95           2 S E1-E3

     FILE 'REGISTRY' ENTERED AT 15:02:54 ON 19 DEC 2000

     FILE 'HCAPLUS' ENTERED AT 15:03:06 ON 19 DEC 2000
L96        3823 S (L6 OR PHOSPHOPROTEIN PHOSPHATASE) AND (PD<=19950809 OR PRD<=
L97           6 S (L6 OR PHOSPHOPROTEIN PHOSPHATASE) AND L7-L21
L98          10 S L96 AND 75/SC,SX
L99          30 S L96 AND ?CRYS?
L100         14 S L96 AND (3D OR THREE DIMENSION?)
L101         25 S L96 AND X RAY
L102        119 S L96 AND CONFORM?
L103         59 S L96 AND  MOLECULAR STRUCTURE
L104        219 S L96 AND L34-L36
L105         25 S L104 AND L97-L103
L106        103 S L97-L101,L103,L105
L107         22 S L96 AND (COMPUT? OR OPTICAL IMAG? OR OPTICAL MEMOR? OR ALGORI
L108         22 S L94 AND L106
L109         42 S L107,L108
L110        124 S L94,L106 NOT L109
L111         19 S L110 AND CRYS?/CW
L112         13 S L110 AND 75/SC,SX
L113         61 S L109,L111,L112
L114        105 S L110 NOT L113
L115        125 S L96 AND L113,L114
L116          1 S L97 NOT L115
L117        126 S L115,L116

=> d bib abs hitrn tot


L117 ANSWER 1 OF 126  HCAPLUS  COPYRIGHT 2000 ACS
AN   1997:723133  HCAPLUS
DN   128:30302
TI   A nonimmunosuppressant FKBP-12 ligand increases nerve regeneration
AU   Gold, Bruce G.; Zeleny-Pooley, Michelle; Wang, Min-Sheng; Chaturvedi,
     Pravin; Armistead, David M.
CS   Center for Research on Occupational and Environmental Toxicology, Oregon
     Health Sciences University, Portland, OR, 97201-3098, USA
SO   Exp. Neurol. (1997), 147(2), 269-278
     CODEN: EXNEAC; ISSN: 0014-4886
PB   Academic
DT   Journal
LA   English
AB   The immunosuppressant drugs FK506 and cyclosporin A inhibit T-cell
     proliferation via a common mechanism: calcineurin inhibition
     following binding to their resp. binding proteins, the peptidyl prolyl
     isomerases FKBP-12 and cyclophilin A.  In contrast, FK506, but not
     cyclosporin A, accelerates nerve regeneration.  In the present study, we
```

show that the potent FKBP-12 inhibitor V-10,367, which lacks the structural components of FK506 required for **calcineurin** inhibition, increases neurite outgrowth in SH-SY5Y neuroblastoma cells and speeds nerve regeneration in the rat sciatic nerve crush model. In SH-SY5Y cells, V-10,367 increased the lengths of neurite processes in a concn.-dependent (between 1 and 10 nM) fashion over time (up to 168 h). Daily s.c. injections of V-10,367 accelerated the onset of clin. signs of functional recovery in the hind feet compared to vehicle-treated control animals. Interdigit distances (between the first and fifth digits) measured on foot prints obtained during walking showed an increase in toe spread in V-10,367-treated rats compared to vehicle-treated controls. Electron microscopy demonstrated larger regenerating axons distal to the crush site in the sciatic nerve from V-10,367-treated rats. Quantitation of axonal areas in the soleus nerve revealed a shift to larger axonal calibers in V-10,367-treated rats (400 or 200 mg/kg/day); mean axonal areas were increased by 52 and 59%, resp., compared to vehicle-treated controls. FKBP-12 ligands lacking **calcineurin** inhibitory activity represent a new class of potential drugs for the treatment of human peripheral nerve disorders.

L117 ANSWER 2 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:367434 HCAPLUS
DN 127:14699
TI Protein phosphatases of fission yeast
AU Yamano, Hiroyuki
CS British Cancer Research Foundation, UK
SO Saibo Shuki (**1995**), 32-33. Editor(s): Taya, Yoichi; Nojima, Hiroshi; Hanaoka, Fumio. Publisher: Yodosha, Tokyo, Japan. CODEN: 64LYAR
DT Conference; General Review
LA Japanese
AB A review with 8 refs. on the **mol. structure**, biol. function, and clin. applications of protein phosphatases of fission yeast.
IT **9025-75-6**, Protein phosphatase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(structure and function of protein phosphatases of fission yeast)

L117 ANSWER 3 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:367293 HCAPLUS
DN 127:2290
TI **Calcineurin**
AU Takahashi, Nobuhiro
CS Res. Inst., Toren Co., Ltd., Japan
SO Saibonai Shigunaru Dentatsu (**1995**), 100-102. Editor(s): Yamamoto, Tadashi. Publisher: Yodosha, Tokyo, Japan. CODEN: 64LXAO
DT Conference; General Review
LA Japanese
AB A review with 11 refs. on the history, **mol. structure**, biol. function, and medical significance of **calcineurin**.
IT **9025-75-6**, **Calcineurin**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(structure and biol. function of)

L117 ANSWER 4 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1997:238395 HCAPLUS
DN 126:222278
TI **Crystal structure** of the active site binding pocket of a **calcineurin** A/**calcineurin** B/**FKBP12**/**FK506** complex and encoded data storage medium capable of graphically display for the design of immunosuppressant inhibitors
IN **Armistead, David M.; Fitzgibbon, Matthew James; Fleming, Mark Andrew; Griffith, James P.; Kim, Eunice E.; Kim, Joseph L.; Sintchak, Michael D.;**

Thomson, John Allan; Wilson, Keith P.
PA Vertex Pharmaceuticals Incorporated, USA
SO PCT Int. Appl., 198 pp.
CODEN: PIXXD2
DT Patent
LA English
FAN.CNT 1

	PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
PI	WO 9706246	A2	19970220	WO 1996-US12818	19960801 <--
	WO 9706246	A3	19970313		
	W: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, UZ, VN, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
	RW: KE, LS, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA				
	AU 9667668	A1	19970305	AU 1996-67668	19960801 <--
	EP 846163	A2	19980610	EP 1996-928071	19960801 <--
	R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, FI				
	JP 11511016	T2	19990928	JP 1996-508623	19960801 <--
PRAI	US 1995-512815	19950809 <--			
	WO 1996-US12818	19960801			

AB The **crystal structure** was detd. and at. **structure** coordinates presented for a complex of N- and C-terminally truncated bovine brain **calcineurin** subunit A (residues 17-392), intact, myristoylated **calcineurin** subunit B (residues 1-168), **FKBP-12** protein (residues 1-107), and the immunosuppressant drug **FK506**, based on **x-ray** diffraction data. **Calcineurin** subunit A is proteolytically digested with clostripain to remove the calmodulin-binding domain and autoinhibitory domain. The **crystals** had an orthorhombic space group symmetry P12121 and unit cell dimensions a = 90 .+-. 5, b = 94 .+-. 6, and c = 117 .+-.5 .ANG.. In resolving the **crystal structure** of bovine brain **calcineurin**, it was found that subunit A amino acid residues 90, 91, 92, 118, 120, 121, 122, 150, 151, 156, 160, 199, 232, 253, 254, 256, 281, 282, 283, 284, 306, 311, 312, and 317 were situated within 8 .ANG. of a phosphate group and 2 metal ions bound to the active site. This invention also relates to a data storage material encoded with the corresponding **structure** coordinates of those **crystd. mols.** or **mol.** complexes. Such data storage material is capable of displaying such mols. and mol. complexes as a graphical 3-dimensional representation on a **computer** screen. In addn., this invention relates to methods of using the **structure** coordinates of those **mols.** or **mol.** complexes to solve the **structure** of homologous proteins. The coordinates can be used to design compds. including immunosuppresant inhibitory compds., that assoc. with **calcineurin** directly or through prior complexation with **FKBP12**.

IT **9025-75-6D, Calcineurin**, complexes with **FKBP12** protein and **FK506 104987-11-3D, FK506**, complexes with **calcineurin** subunits A and B and **FKBP12** protein
RL: BUU (Biological use, unclassified); PRP (Properties); BIOL (Biological study); USES (Uses)
(**crystal structure** of the active site binding pocket of a **calcineurin** A/**calcineurin** B/**FKBP12/FK506** complex and encoded data storage medium capable of graphically display for the design of immunosuppressant inhibitors)

L117 ANSWER 5 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:10916 HCAPLUS
DN 124:49436

TI **Crystal structure** of the catalytic subunit of human protein phosphatase 1 and its complex with tungstate
AU Egloff, Marie-Pierre; Cohen, Patricia T. W.; Reinemer, Peter; Barford, David
CS Lab. Mol. Biophys., Univ. Oxford, Oxford, OX1 3QU, UK
SO J. Mol. Biol. (**1995**), 254(5), 942-59
CODEN: JMOBAK; ISSN: 0022-2836
DT Journal
LA English
AB **Phosphoprotein phosphatase** 1 (PP1) is a serine/threonine **phosphoprotein phosphatase** that is essential in regulating diverse cellular processes. Here, the authors report the **crystal structure** of the catalytic subunit of human PP1.gamma.1 and its complex with tungstate at 2.5 .ANG. resoln. The anomalous scattering from tungstate was used in a multiple wavelength anomalous dispersion expt. to derive **crystallog**. phase information. The protein adopted a single domain with a novel fold, distinct from that of the phosphoprotein tyrosine phosphatases. A dinuclear ion center consisting of Mn2+ and Fe2+ was situated at the catalytic site that bound the phosphate moiety of the substrate. Proton-induced **x-ray** emission spectroscopy was used to identify the nature of the ions bound to the enzyme. The structural data indicated that dephosphorylation was catalyzed in a single step by a metal-activated water mol. This contrasted with other phosphatases, including phosphoprotein tyrosine phosphatases, and acid and alk. phosphatases which form phosphoryl-enzyme intermediates. The **structure** of PP1 provided insight into the **mol**. mechanism for substrate recognition, enzyme regulation and inhibition of this enzyme by toxins and tumor promoters and a basis for understanding the expanding family of related phosphatases which include PP2A and PP2B (**calcineurin**).
IT **9025-75-6, Phosphoprotein phosphatase**
RL: PRP (Properties)
(1, catalytic subunit; **crystal structure** of the catalytic subunit of human **phosphoprotein phosphatase** 1 and its complex with tungstate)
IT **9025-75-6D, Phosphoprotein phosphatase**, 1, catalytic subunit, tungstate complexes
RL: PRP (Properties)
(**crystal structure** of the catalytic subunit of human **phosphoprotein phosphatase** 1 and its complex with tungstate)

L117 ANSWER 6 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1996:4838 HCAPLUS
DN 124:48884
TI Protein phosphatases
AU Barford, David
CS University of Oxford, Oxford, UK
SO Curr. Opin. Struct. Biol. (**1995**), 5(6), 728-34
CODEN: COSBEF; ISSN: 0959-440X
DT Journal; General Review
LA English
AB A review with 64 refs. Protein phosphatases are signal transducing enzymes that dephosphorylate cellular phosphoproteins. The recently detd. **crystal** structures of protein tyrosine and serine/threonine phosphatases reveal that these proteins adopt distinct structures and catalyze dephosphorylation reactions by different enzymic mechanisms. Insights into the basis for substrate specificity and enzyme regulation can also be gained from these **crystal** structures.
IT **9025-75-6**, Serine/threonine phosphatase
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(protein phosphatases)

L117 ANSWER 7 OF 126 HCAPLUS COPYRIGHT 2000 ACS

AN 1995:1001176 HCAPLUS
DN 124:176907
TI Synthetic Tyr-phospho and non-hydrolyzable phosphonopeptides as PTKs and TC-PTP inhibitors
AU Ruzza, Paolo; Deana, Arianna Donella; Calderan, Andrea; Pavanetto, Michela; Cesaro, Luca; Pinna, Lorenzo A.; Borin, Gianfranco
CS Biopolymers Res. Cent., Univ. Padua, Padua, Italy
SO Int. J. Pept. Protein Res. (**1995**), 46(6), 535-46
CODEN: IJPPC3; ISSN: 0367-8377
DT Journal
LA English
AB Tyrosine-specific protein kinases and phosphatases are important signal transducing enzymes to normal cellular growth and differentiation and have been implicated in the etiol. of a no. of human neoplastic processes. In order to develop agents which inhibit the function of these two classes of enzymes by interfering with the binding of their substrates, the authors synthesized analogs derived from the peptide H-Glu-Asp-Asn-Glu-Tyr-Thr-Ala-OH. This sequence reproduces the main autophosphorylation site of Src tyrosine kinases. In this work the synthesis, by classical soln. methods, of the phosphotyrosyl peptide H-Glu-Asp-Asn-Glu-Tyr-Thr(PO3H2)-Ala-OH, as well as of three analogs in which the phosphotyrosine is replaced by a phosphinotyrosine and by two unnatural, nonhydrolyzable amino acids 4-phosphonomethyl-L-phenylalanine and 4-phosphono-L-phenylalanine (Pphe), is reported. The Src peptide and its derivs. were tested as inhibitors of three non-receptor tyrosine kinases (Lyn, belonging to the Src family, CSK and PTK-IIB) and a nonreceptor protein tyrosine phosphatase obtained from human T-cell (TC-PTP). The biomimetic analogs, which do not significantly affect the activity of CSK, PTK-IIB and TC-PTP, act as efficient inhibitors on Lyn, influencing both the exogenous phosphorylation and, esp., its autophosphorylation. In particular, the Pphe deriv. may provide a basis for the design of a class of inhibitors specific for Lyn and possibly Src tyrosine kinases, capable of being used in vivo and in vitro conditions.

L117 ANSWER 8 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:984239 HCAPLUS
DN 124:80577
TI **Crystal structures** of human **calcineurin** and the human **FKBP12-FK506-calcineurin** complex
AU Kissinger, Charles R.; Parge, Hans E.; Knighton, Daniel R.; Lewis, Cristina T.; Pelletier, Laura A.; Tempczyk, Anna; Kalish, Vincent J.; Tucker, Kathleen D.; Showalter, Richard E.; et al.
CS Agouron Pharmaceuticals Inc., San Diego, CA, 92121-1121, USA
SO Nature (London) (**1995**), 378(6557), 641-4
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB **Calcineurin** (CaN) is a calcium- and calmodulin-dependent protein serine/threonine phosphatase which is crit. for several important cellular processes, including T-cell activation. CaN is the target of the immunosuppressive drugs cyclosporin A and **FK506**, which inhibit CaN after forming complexes with cytoplasmic binding proteins (cyclophilin and **FKBP12**, resp.). The authors report here the **crystal structures** of full-length human CaN at 2.1 .ANG. resoln. and of the complex of human CaN with **FKBP12-FK506** at 3.5 .ANG. resoln. In the native CaN **structure**, an autoinhibitory element binds at the Zn/Fe-contg. active site. The site of binding of **FKBP12-FK506** appears to be shared by other non-competitive inhibitors of **calcineurin**, including a natural anchoring protein.
IT **9025-75-6, Calcineurin**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(**crystal structures** of human **calcineurin** and the human **FKBP12-FK506-calcineurin** complex)

IT **104987-11-3, FK506**
RL: PRP (Properties)
(**crystal structures** of human **calcineurin** and the human **FKBP12-FK506-calcineurin** complex)

L117 ANSWER 9 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:976138 HCAPLUS
DN 124:24251
TI NMR identification of **calcineurin** B residues affected by binding of a **calcineurin** A peptide
AU Anglister, Jacob; Ren, Hao; Klee, Claude B.; Bax, Ad
CS Laboratory of Chemical Physics, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, MD, 20892-0520, USA
SO FEBS Lett. (**1995**), 375(1,2), 108-12
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English
AB Triple resonance **3D** NMR methods have been used to study the interaction between **calcineurin** B and a peptide fragment of **calcineurin** A for which it has high affinity (KD .apprx. 4.times.10-7 M). Although **calcineurin** B aggregates at NMR concns. of .apprx. 1 mM, in the presence of a target peptide fragment of **calcineurin** A it becomes monomeric and yields NMR spectra that are very similar to those reported previously for **calcineurin** B solubilized by the zwitterionic detergent CHAPS. Changes in chem. shifts between CHAPS- and peptide-solubilized **calcineurin** B are small which is indicative of no differences in secondary structure. Residues most affected by binding to target peptide are found primarily on the hydrophobic faces of the four helixes, present in each of the two globular domains in **calcineurin** B, and in the loops connecting helixes II and III, IV and V, and possibly in the C-terminal 12 residues, which also exhibit a change in mobility.
IT **9025-75-6, Calcineurin**
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(A and B; NMR identification of **calcineurin** boron residues affected by binding of **calcineurin** peptide)

L117 ANSWER 10 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:950149 HCAPLUS
DN 124:24647
TI Transition state and rate-limiting step of the reaction catalyzed by the human dual-specificity phosphatase, VHR
AU Zhang, Zhong-Yin; Wu, Li; Chen, Li
CS Department of Molecular Pharmacology, Albert Einstein College of Medicine, Bronx, NY, 10461, USA
SO Biochemistry (**1995**), 34(49), 16088-96
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB The dual-specificity phosphatases are unusual catalysts in that they can utilize protein substrates contg. phosphotyrosine as well as phosphoserine/threonine. The dual-specificity phosphatases and the protein-tyrosine phosphatases (PTPases) share the active site motif (H/V)C(X)5R(S/T), but display little amino acid sequence identity outside of the active site. Although the dual-specificity phosphatases and the PTPases appear to bring about phosphate monoester hydrolysis through a similar mechanism, it is not clear what causes the difference in the active-site specificity between the two groups of enzymes. In this paper, the authors show that the human dual-specificity phosphatase, VHR [for VH1-related], is rather promiscuous toward small phosphate monoesters (including both aryl and alkyl phosphates of primary alcs.) with effectively identical kcat/Km and kcat values while the pKa values of the leaving groups (phenols or alcs.) varied from 7 to 16. Linear free-energy

relation anal. of kcat and kcat/Km of the enzyme-catalyzed hydrolysis reaction suggests that a uniform mechanism is utilized for both the aryl and alkyl substrates. The very small dependency of kcat/Km on the leaving group pKa can be accounted for by the protonation of the leaving group. Pre-steady-state burst kinetic anal. of the VHR-catalyzed hydrolysis of p-nitrophenyl phosphate provides direct kinetic evidence for the involvement of a phosphoenzyme intermediate in the dual specificity phosphatase-catalyzed reaction. The rate-limiting step for the VHR-catalyzed hydrolysis of p-nitrophenyl phosphate corresponds to the decompn. of the phosphoenzyme intermediate. Results from kinetic solvent isotope effects on the formation (kH2O/kD2O = 0.52) and the breakdown (kH2O/kD2O = 1.15) of the phosphoenzyme intermediate are consistent with a highly dissociative metaphosphate-like transition state for both steps, where bond formation to the incoming nucleophile is minimal and bond breaking between phosphorus and the leaving group is substantial. To promote and stabilize the dissociative transition state, the proton from the putative general acid Asp92 is largely transferred to the bridge oxygen atom in the transition state.

IT **9025-75-6, Phosphoprotein phosphatase**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(VHR; transition state and rate-limiting step of reaction catalyzed by human dual-specificity phosphatase, VHR)

L117 ANSWER 11 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:945940 HCAPLUS
DN 124:75855
TI **Structure** comparison of native and mutant human recombinant **FKBP12** complexes with the immunosuppressant drug **FK506** (**tacrolimus**)
AU Itoh, Susumu; Navia, Manuel A.
CS Vertex Pharmaceuticals Incorporated, Cambridge, MA, 02139-4211, USA
SO Protein Sci. (**1995**), 4(11), 2261-8
CODEN: PRCIEI; ISSN: 0961-8368
DT Journal
LA English
AB The consequences of site-directed mutagenesis expts. are often anticipated by empirical rules regarding the expected effects of a given amino acid substitution. The effects of conservative and nonconservative substitutions on the **x-ray crystal structures** of human recombinant **FKBP12** mutants complexed with **FK506** were examd. R42K and R42I mutant complexes showed 110-fold- and 180-fold-decreased **calcineurin** inhibition, resp., vs. the native complex, yet retained full peptidyl prolyl isomerase (PPIase) activity, **FK506** binding, and **FK506**-mediated PPIase inhibition. The **structure** of the R42I mutant complex was better conserved than that of the R42K mutant complex when compared to the native complex **structure**, within both the **FKBP12** protein and **FK506** ligand regions of the complexes, and with respect to temp. factors and RMS coordinate differences. This is due to compensatory interactions mediated by 2 newly ordered water **mols**. in the R42I complex **structure**, **mols**. that act as surrogates for the missing arginine guanidino nitrogens of R42. The absence of such surrogate solvent interactions in the R42K complex leads to some disorder in the 40s loop (residues 40-44 of **FKBP12**) that encompasses the substituent. One rationalization for the obsd. loss in **calcineurin** inhibition in these R42 mutant complexes invokes indirect effects leading to a misorientation of **FKBP12** and **FK506** structural elements that normally interact with **calcineurin**. The results with the **structure** of the R42I complex in particular suggest that the obsd. loss of **calcineurin** inhibition might also be explained by the loss of a specific R42-mediated interaction with **calcineurin** that cannot be mimicked effectively by the solvent **mols**. that otherwise stabilize the **conformation** of the 40s loop in that **structure**.

IT **9025-75-6, Calcineurin**

RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(**structure** comparison of native and mutant human recombinant **FKBP12** complexes with immunosuppressant drug **FK506**)

IT **104987-11-3D, FK 506**, complexes with protein **FKBP12**
RL: PRP (Properties)
(**structure** comparison of native and mutant human recombinant **FKBP12** complexes with immunosuppressant drug **FK506**)

L117 ANSWER 12 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:912941 HCAPLUS
DN 123:333684
TI Preliminary **crystallization** studies of calmodulin-dependent protein phosphatase (**calcineurin**) from bovine brain
AU Balendiran, K.; Tan, Yingchun; Sharma, Rajendra K.; Murthy, Krishna H. M.
CS Fels Inst. Cancer Research Molecular Biology, Temple Univ. School Medicine, Philadelphia, PA, 19140, USA
SO Mol. Cell. Biochem. (**1995**), 149 & 150, 127-30
CODEN: MCBIB8; ISSN: 0300-8177
DT Journal
LA English
AB **Calcineurin** is a serine/threonine protein phosphatase which catalyzes the hydrolysis of both phosphoseryl/phosphothreonyl and phosphotyrosyl proteins as well as low mol. wt. compds. such as p-nitrophenyl phosphate. It is a hetero-dimeric protein consisting of a 60 kDa A chain and 19 kDa B chain. **Calcineurin** A is organized into functionally distinct domains such as a catalytic domain, a **calcineurin** B binding domain, a calmodulin-binding domain, and an inhibitory domain. **Calcineurin** B has four EF-hand calcium binding domains with a secondary **structure** that is homologous to calmodulin but its metal binding properties are more similar to troponin-C. The N-terminal myristoyl group of **calcineurin** B might play a role in the interaction between subunits A and B during phosphorylation/dephosphorylation processes. **Crystals** of size 0.125.times.0.07.times.0.03 mm and 0.7.times.0.03.times.0.02 mm have been obtained for **calcineurin** and the A subunit resp. **Crystals** of **calcineurin** show strong diffraction to 5.3 .ANG. and weak diffraction to 3.0 .ANG. on rotating anode operated at 50 kV and 100 mA. Further work is in progress to improve the **x-ray** diffraction quality of these **crystals** and to obtain well diffracting **crystals** of **calcineurin** B.

IT **9025-75-6, Phosphoprotein phosphatase**
RL: PEP (Physical, engineering or chemical process); PRP (Properties); PROC (Process)
(**calcineurin**; preliminary **crystn**. studies of calmodulin-dependent protein phosphatase (**calcineurin**) from bovine brain)

L117 ANSWER 13 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:912323 HCAPLUS
DN 123:333510
TI Phosphonate inhibitors of protein-tyrosine and serine/threonine phosphatases
AU Kole, Hemanta K.; Smyth, Mark S.; Russ, Pamela L.; Burke, Terrence R., Jr.
CS Diabetes Univ., National Inst. Aging, Baltimore, MD, 21224, USA
SO Biochem. J. (**1995**), 311(3), 1025-31
CODEN: BIJOAK; ISSN: 0264-6021
DT Journal
LA English
AB In all, 15 aryl-contg. phosphonates have been synthesized and tested for their effect on protein-tyrosine phosphatase (PTPase) activity. Two compds., (naphth-2-yl) difluoromethylphosphonic acid (12) and (naphthy-1-yl) difluoromethylphosphonic acid (13) have been found to inhibit dephosphorylation of [32P]insulin receptors by PTP-1B, a protein tyrosine phosphatase (PTPase), with IC50 values of 40-50 .mu.M. Compd. 12 competitively inhibited insulin-receptor dephosphorylation by PTP-1B.

Compd. 12 also inhibited PTP-1B-catalyzed dephosphorylation of a synthetic tyrosine phosphorylated substrate poly(Glu80-Tyr20) at the same potency, indicating that 12 acted via interaction with the PTPase. Addnl., 12 inhibited insulin-receptor PTPase(s) and epidermal-growth-factor-receptor PTPase(s) present in solubilized membranes from CHO (Chinese-hamster ovary)/HIRc and A431 cells resp. IC50 values of 40-50 .mu.M were obtained in all cases with compd. 12. Of note is the fact that these compds. did not have any effect on insulin-receptor autophosphorylation. Nine out of the 15 compds. potently inhibited serine/threonine phosphatase PP-2A activity without any effect on serine/threonine phosphatase PP-1 when tested at a concn. as high as 675 .mu.M. The most potent compds. acting toward PP-2A had IC50 values of 45-50 .mu.M. These PP-2A inhibitors could be useful tools for studying serine/threonine-phosphatase-mediated signal transduction. Two compds., 12 and 13, inhibited both tyrosine phosphatase PTP-1B and serine/threonine phosphatase PP-2A with similar potency; IC50 values being 40-50 .mu.M in both cases. Details of the synthesis of compds. 10, 11 and 13 are given in Supplementary Publication SUP 50177 (6 pages), which has been deposited at the British Library Document Supply Center, Boston Spa, Wetherby, West Yorkshire LS23 7BQ, U.K., from whom copies can be obtained on the terms indicated in Biochem. J. (1995) 305, 9.

IT **9025-75-6**, Serine/threonine phosphatase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(phosphonate inhibitors of protein-tyrosine and serine/threonine phosphatases)

L117 ANSWER 14 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:880621 HCAPLUS
DN 124:22664
TI Toward a cDNA map of the human genome
AU Korenberg, Julie R.; Chen, Xiao-Ning; Adams, Mark D.; Venter, J. Craig
CS Ahmanson Department of Pediatrics, Cedars-Sinal Research Institute, Los Angeles, CA, 90048, USA
SO Genomics (**1995**), 29(2), 364-70
CODEN: GNMCEP; ISSN: 0888-7543
DT Journal
LA English
AB Advances in the Human Genome Project are shaping the strategies for identifying the 50,000-100,000 human genes. High-resoln. genetic maps of the human genome combined with sequencing herald an era of rapid regional definition of disease genes. However, only once their chromosome band location is known will the systematic partial sequencing of thousands of random cDNA clones provide the reagents for the rapid assessment of the genes responsible for the inherited disorders. We now present an approach to the rapid detn. of map position and therefore to the creation of a transcribed map of the human genome. Sensitive fluorescence in situ hybridization has been combined with high-resoln. chromosome banding and random cDNA sequencing to map 41 cDNAs with an av. insert size of <2 kb to single human chromosome bands. The results provide 15 new genes, with **database** and functional information, as candidates for human disease. These include the large extracellular signal-related kinase (HUMERK), the ERK activator kinase (PRKMK1), a new member of the RAS oncogene family, protein phosphatase 2 regulatory subunit B alpha isoform (PPP2R2A), and a novel human gene with very high homol. to a plant membrane transport family. Further, an anal. of expressed genes assocd. with pseudogenes showed that by using these techniques, it is possible to detect accurately the transcribed locus within a multigene or processed pseudogene family in most cases. These findings suggest that direct cDNA mapping using fluorescence in situ hybridization provides an accurate and rapid approach to the definition of a transcribed map of the human genome. This low-cost, high-resoln. (2-5 Mb) mapping greatly enhances the speed with which these genes can be subsequently assigned to contigs. This assignment provides a necessary first step in understanding the relation of the genes to both acquired and inherited human diseases.

IT **9025-75-6**, Protein phosphatase
RL: BSU (Biological study, unclassified); BIOL (Biological study)

(2A; application of fluorescence in situ hybridization (FISH) towards a cDNA map of human genome)

L117 ANSWER 15 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:874334 HCAPLUS
DN 124:87734
TI A medicinal chemistry evaluation of the autoinhibitory domain of **calcineurin**
AU Rivetna, Meheryar N.; Salowe, Scott P.; Tolman, Richard L.; Jones, A. Brian
CS Departments Synthetic Chemical Research Molecular Design & Diversity, Merck Research Laboratories, Rahway, NJ, 07065, USA
SO Bioorg. Med. Chem. Lett. (**1995**), 5(11), 1147-50
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB Truncation of, and substitutions in, the 25 amino acid autoinhibitory element of the phosphatase **calcineurin** indicate that most of the segment is required for inhibition. The peptide does not, therefore, represent a convenient starting point for small mol. drug development.
IT **9025-75-6DP, Calcineurin**, fragment, analogs
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(prepn. and evaluation of autoinhibitory domain of **calcineurin**
)

L117 ANSWER 16 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:860483 HCAPLUS
DN 123:278299
TI Modulation of the stress-induced synthesis of stress proteins by a phorbol ester and okadaic acid
AU Ito, Hidenori; Hasegawa, Kaori; Inaguma, Yutaka; Kozawa, Osamu; Asano, Tomiko; Kato, Kanefusa
CS Dep. Biochem., Aichi Human Serv. Cent., Aichi, 480-03, Japan
SO J. Biochem. (Tokyo) (**1995**), 118(3), 629-34
CODEN: JOBIAO; ISSN: 0021-924X
DT Journal
LA English
AB The expression of .alpha.B **crystallin**, hsp27, and hsp70 in C6 cells increased when the cells were exposed to arsenite (50 .mu.M for 1 h) or heat (42.degree.C for 30 min), as detected by specific immunoassays, Western blot anal., and Northern blot anal. When cells were exposed to arsenite in the presence of 0.1 .mu.M phorbol 12-myristate 13-acetate (PMA), an activator of protein kinase C, or 0.2 .mu.M okadaic acid, an inhibitor of phosphoserine/phosphothreonine protein phosphatases, expression of .alpha.B **crystallin** was markedly enhanced. The induction of hsp27 and hsp70 expression was also stimulated to a considerable extent in the same cells. The stimulatory effect of PMA was further enhanced in the presence of okadaic acid, but it was strongly inhibited in the presence of 0.5 .mu.M staurosporine, an inhibitor of protein kinase C. PMA and okadaic acid also stimulated the response to heat stress of the expression of .alpha.B **crystallin**, but they barely stimulated the response to heat stress of hsp27. The extent of stimulation of the arsenite-induced responses by PMA and okadaic acid was greater when the concn. of arsenite (i.e. the magnitude of the stress) was relatively low (25-50 .mu.M). The arsenite-induced release of arachidonic acid from cells was also stimulated in the presence of PMA and/or okadaic acid, and the stimulatory effects of PMA and okadaic acid on the arsenite-induced accumulation of .alpha.B **crystallin** and hsp27 were strongly suppressed by quinacrine, an inhibitor of phospholipase A2. These results suggest that the stimulatory effects of PMA and okadaic acid on the stress responses are caused, in part, by the increased metabolic activity of the arachidonic acid cascade, as a consequence of the activation of phospholipase A2.
IT **9025-75-6**, Protein phosphatase
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)

(stress-induced synthesis of stress proteins in relation to protein kinase C and phosphoserine/phosphothreonine protein phosphatase)

L117 ANSWER 17 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:796298 HCAPLUS
DN 123:246308
TI **Conformation** of **FK506** in **x-ray** structures of its complexes with human recombinant FKBP12 mutants
AU Itoh, Susumu; DeCenzo, Maureen T.; Livingston, David J.; Pearlman, David A.; Navia, Manuel A.
CS Vertex Pharmaceuticals Incorporated, Cambridge, MA, 02139-4211, USA
SO Bioorg. Med. Chem. Lett. (**1995**), 5(17), 1983-8
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB In the **x-ray** structure of the **FK506** complex with an FKBP12 double-mutant (R42K + H87V), the ligand is seen to adopt a **conformation** in its effector domain region that is distinctly altered compared to that found in the compd. structure with native FKBP12. Nonetheless, mol. dynamics simulations indicate that the **FK506 conformations** seen in the native and mutant complex structures are energetically equiv. Our observations suggest caution in the application of drug design strategies for **calcineurin**-mediated immunosuppressants that are based on mimicry of the **FK506 conformation** seen in the structure of the ligand complex with native FKBP12.
IT **104987-11-3, FK506**
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(**conformation** of **FK506** in **x-ray** structures of its complexes with human recombinant FKBP12 mutants)

L117 ANSWER 18 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:794212 HCAPLUS
DN 123:192273
TI **Three-dimensional structure** of the catalytic subunit of protein serine/threonine phosphatase-1
AU Goldberg, Jonathan; Huang, Hsien-bin; Kwon, Young-guen; Greengard, Paul; Nairn, Angus C.; Kuriyan, John
CS Howard Hughes Med. Inst., Rockefeller Univ., New York, NY, 10021, USA
SO Nature (London) (**1995**), 376(6543), 745-53
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB The **crystal structure** of mammalian (rabbit muscle) **phosphoprotein phosphatase** 1, complexed with the toxin, microcystin, and detd. at 2.1 .ANG. resoln., revealed that it is a metalloenzyme unrelated in architecture to the phosphoprotein tyrosine phosphatases. Two metal cations were positioned by a central .beta.-.alpha.-.beta.-.alpha.-.beta. scaffold at the active site, from which emanate 3 surface grooves that are potential binding sites for substrates and inhibitors. The C-terminus was positioned at the end of one of the grooves such that regulatory sequences following the domain might modulate function. The fold of the catalytic domain was expected to be closely preserved in **phosphoprotein phosphatases** 2A and 2B (**calcineurin**).
IT **9025-75-6, Phosphoprotein phosphatase**
RL: PRP (Properties)
(1, catalytic subunit; **crystal structure** of the catalytic subunit of **phosphoprotein phosphatase** 1)
IT **9025-75-6DP, Phosphoprotein phosphatase**, 1, catalytic subunit, microcystin complexes
RL: PRP (Properties); SPN (Synthetic preparation); PREP (Preparation)
(**crystal structure** of the catalytic subunit of **phosphoprotein phosphatase** 1)

L117 ANSWER 19 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:750348 HCAPLUS
DN 123:188015
TI **X-ray structure** of **calcineurin** inhibited by the immunophilin-immunosuppressant **FKBP12-FK506** complex
AU **Griffith, James P.**; **Kim, Joseph L.**; **Kim, Eunice E.**; **Sintchak, Michael D.**; **Thomson, John A.**; **Fitzgibbon, Matthew J.**; **Fleming, Mark A.**; Caron, Paul R.; Hsiao, Kathy; Navia, Manuel A.
CS Vertex Pharmaceuticals, Incorporated, Cambridge, MA, 02139-4211, USA
SO Cell (Cambridge, Mass.) (**1995**), 82(3), 507-22
CODEN: CELLB5; ISSN: 0092-8674
DT Journal
LA English
AB The **x-ray structure** of the ternary complex of a **calcineurin** A fragment, **calcineurin** B, **FKBP12**, and the immunosuppressant drug **FK506** (also known as **tacrolimus**) has been detd. at 2.5 .ANG. resoln., providing a description of how **FK506** functions at the at. level. In the **structure**, **FKBP-12**-KF506 binary complex does not contact the phosphatase active site on **calcineurin** A that is more than 10 .ANG. removed. Instead, **FKBP-12-FK506** is so positioned that it can inhibit the dephosphorylation of its macromol. substrates by phys. hindering their approach to the active site. The ternary complex described here represents the **three-dimensional structure** of a Ser/Thr protein phosphatase and provides a structural basis for understanding **calcineurin** inhibition by **FKBP-12-FK506**.
IT **9025-75-6**, **Calcineurin 104987-11-3**, **FK506**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**crystal structure** of ternary complexes of **calcineurin**, **FK506**, and **FKBP12** and mechanism of immunosuppressant action)

L117 ANSWER 20 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:749219 HCAPLUS
DN 123:217939
TI Design, synthesis and **structure** of non-macrocyclic inhibitors of **FKBP12**, the major binding protein for the immunosuppressant **FK506**
AU **Armistead, D. M.**; Badia, M. C.; Deininger, D. D.; Duffy, J. P.; Saunders, J. O.; Tung, R. D.; **Thomson, J. A.**; DeCenzo, M. T.; Futer, O.; et al.
CS Vertex Pharmaceuticals Incorporated, Cambridge, MA, 02139-4211, USA
SO Acta Crystallogr., Sect. D: Biol. Crystallogr. (**1995**), D51(4), 522-8
CODEN: ABCRE6; ISSN: 0907-4449
DT Journal
LA English
AB The authors have synthesized a series of non-macrocyclic ligands to **FKBP12** that are comparable in binding potency and peptidyl prolyl isomerase (PPIase) inhibition to **FK506** itself. The authors have also solved the **structure** of one of these ligands in complex with **FKBP12**, and have compared that **structure** to the **FK506-FKBP12** complex. Consistent with the obsd. inhibitory equipotency of these compds., the authors observe a strong similarity in the **conformation** of the two ligands in the region of the protein that mediates PPIase activity. The compds., however, are not immunosuppressive. In the **FKBP12-FK506** complex, a significant portion of the **FK506** ligand, its 'effector domain', projects beyond the envelope of the binding protein in a manner that is suggestive of a potential interaction with a second protein, the calcium-dependent phosphatase, **calcineurin**, whose inhibition by

the **FKBP12-FK506** complex interrupts the T-cell activation events leading to immunosuppression. In contrast, the compds. bind within the surface envelope of **FKBP12**, and induce significant changes in the **structure** of the **FKBP12** protein which may also affect **calcineurin** binding indirectly.

IT **9025-75-6, Calcineurin**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(anal. of the interaction between **FKBP12** and non-macrocyclic ligands by **X-ray crystallog.** in relation to **calcineurin**)

IT **104987-11-3, FK506**
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(anal. of the interaction between **FKBP12** and non-macrocyclic ligands in relation to the interaction between **FKBP12** and the immunosuppressant **FK506**)

L117 ANSWER 21 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:749218 HCAPLUS
DN 123:217708
TI Comparative **x-ray** structures of the major binding protein for the immunosuppressant **FK506** (**Tacrolimus**) in unliganded from and in complex with **FK506** and rapamycin
AU **Wilson, Keith P.**; Yamashita, Mason M.; **Sintchak, Michael D.**; Rotstein, Sergio H.; Murcko, Mark A.; Boger, Joshua; **Thomson, John A.**; **Fitzgibbon, Matthew J.**; Black, James R.; et al.
CS Vertex Pharmaceuticals Incorporated, Cambridge, MA, 02139-4211, USA
SO Acta Crystallogr., Sect. D: Biol. Crystallogr. (**1995**), D51(4), 511-21
CODEN: ABCRE6; ISSN: 0907-4449
DT Journal
LA English
AB **FK506** (**tacrolimus**) is a natural product now approved in the US and Japan for organ transplantation. **FK506**, in complex with its 12 kDa cytosolic receptor (**FKBP12**), is a potent agonist of immunosuppression through the inhibition of the phosphatase activity of **calcineurin**. Rapamycin (sirolimus), which is itself an immunosuppressant by a different mechanism, completes with **FK506** for binding to **FKBP12** and thereby acts as an antagonist of **calcineurin** inhibition. The authors have solved the **x-ray** structure of unliganded **FKBP12** and **FKBP12** in complex with **FK506** and with rapamycin; these structures show localized differences in **conformation** and mobility in those regions of the protein that are known, by site-directed mutagenesis, to be involved in **calcineurin** inhibition. A comparison of 16 addnl. **x-ray** structures of **FKBP12** in complex with **FKBP12**-binding ligands, where those structures were detd. from different **crystal** forms with distinct packing arrangements, lends significance to the obsd. structural variability and suggests that it represents an intrinsic functional characteristic of the protein. Similar differences have been obsd. for **FKBP12** before, but were considered artifacts of **crystal** -packing interactions. The authors suggest that immunosuppressive ligands express their differential effects in part by modulating the **conformation** of **FKBP12**, in agreement with mutagenesis expts. on the protein, and not simply through differences in the ligand structures themselves.

IT **104987-11-3, FK506**
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(**x-ray** structures of the major binding protein for immunosuppressant **FK506** (**Tacrolimus**) in unliganded from and in complex with **FK506** and rapamycin)

L117 ANSWER 22 OF 126 HCAPLUS COPYRIGHT 2000 ACS

AN 1995:748246 HCAPLUS
DN 123:307705
TI New open reading frames, one of which is similar to the nifV gene of Azotobacter vinelandii, found on a 12.5 kbp fragment of chromosome IV of Saccharomyces cerevisiae
AU Verhasselt, Peter; Voet, Marleen; Volckaert, Guido
CS Lab. Gene Technol., Univ. Leuven, Louvain, B-3001, Belg.
SO Yeast (**1995**), 11(10), 961-6
CODEN: YESTE3; ISSN: 0749-503X
DT Journal
LA English
AB The nucleotide sequence of a 12.5 kbp segment of the left arm of chromosome IV is described. Five open reading frames (ORFs) longer than 100 amino acids were detected, all of which are completely confined to the 12.5 kbp region. Two ORFs (D1271 and D1286) correspond to previously sequenced genes (PPH122 and VMA1 or TFP1, resp.). ORF D1298 shows the characteristics of .alpha.-isopropylmalate and homocitrate synthase genes and is similar to the nifV gene of Azotobacter vinelandii. Two more ORFs have no apparent homolog in the data libraries. Conversely, two smaller ORFs of 25 and 85 amino acids encoding the ribosomal protein YL41A and an ATPase inhibitor, resp., were detected. Although a substantial part of the 12.5 kbp fragment apparently lacks protein-coding characteristics, no other elements, such as tRNA genes or transposons, were found. The nucleotide sequence data reported in this paper will appear in the EMBL, GenBank and DDBJ nucleotide sequence **databases** under the accession no. X83276.
IT **9025-75-6**, Protein phosphatase
RL: PRP (Properties)
(gene PPH22; genes of 12.5 kbp fragment of chromosome IV left arm of Saccharomyces cerevisiae)

L117 ANSWER 23 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:747086 HCAPLUS
DN 123:333618
TI **FK506** binding protein mutational analysis. Defining the surface residue contributions to stability of the **calcineurin** co-complex
AU Futer, Olga; DeCenzo, Maureen T.; Aldape, Robert A.; Livingston, David J.
CS Vertex Pharmaceuticals Inc., Cambridge, MA, 02139-4211, USA
SO J. Biol. Chem. (**1995**), 270(32), 18935-40
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The 12- and 13-kDa **FK506** binding proteins (FKBP12 and FKBP13) are cis-trans peptidyl-prolyl isomerases that bind the macrolides **FK506** (**Tacrolimus**) and rapamycin (Sirolimus). The FKBP12.cntdot.**FK506** complex is immunosuppressive, acting as an inhibitor of the protein phosphattase **calcineurin**. We have examd. the role of the key surface residues of FKBP12 and FKBP13 in **calcineurin** interactions by generating substitutions at these residues by site-directed mutagenesis. All mutants are active catalysts of the prolyl isomerase reaction, and bind **FK506** or rapamycin with high affinity. Mutations at FKBP12 residues Asp-37, Arg-42, His-87, and Ile-90 decrease **calcineurin** affinity of the mutant FKBP12.cntdot.**FK506** complex by as much as 2600-fold in the case of I90K. Replacement of three FKBP13 surface residues (Gln-50, Ala-95, and Lys-98) with the corresponding homologous FKBP12 residues (Arg-42, His-87, and Ile-90) generates an FKBP13 variant that is equiv. to FKBP12 in its affinity for **FK506**, rapamycin, and **calcineurin**. These results confirm the role of two loop regions of FKBP12 (residues 40-44 and 84-91) as part of the effector face that interacts with **calcineurin**.
IT **9025-75-6, Calcineurin**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(defining surface residue contributions to stability of **calcineurin**-FKBP complex by **FK506** binding protein mutational anal.)

L117 ANSWER 24 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:664755 HCAPLUS
DN 123:279616
TI Targets of immunophilin-immunosuppressant complexes are distinct highly conserved regions of **calcineurin** A
AU Cardenas, Maria; Muir, R. Scott; Breuder, Tamara; Heitman, Joseph
CS Dep. Genet. Pharmacol., Duke Univ. Med. Cent., Durham, NC, 27710, USA
SO EMBO J. (**1995**), 14(12), 2772-83
CODEN: EMJODG; ISSN: 0261-4189
DT Journal
LA English
AB The immunosuppressive complexes cyclophilin A-cyclosporin A (CsA) and FKBP12-**FK506** inhibit **calcineurin**, a heterodimeric Ca2+-calmodulin-dependent protein phosphatase that regulates signal transduction. The authors have characterized CsA- or **FK506** -resistant mutants isolated from a CsA-**FK506**-sensitive Saccharomyces cerevisiae strain. Three mutations that confer dominant CsA resistance are single amino acid substitutions (T350K, T350R, Y377F) in the **calcineurin** A catalytic subunit CMP1. One mutation that confers dominant **FK506** resistance alters a single residue (W430C) in the **calcineurin** A catalytic subunit CMP2. In vitro and in vivo, the CsA-resistant **calcineurin** mutants bind FKBP12-**FK506** but have reduced affinity for cyclophilin A-CsA. When introduced into the CMP1 subunit, the **FK506** resistance mutation (W388C) blocks binding by FKBP12-**FK506**, but not by cyclophilin A-CsA. Co-expression of CsA-resistant and **FK506**-resistant **calcineurin** A subunits confers resistance to CsA and to **FK506** but not to CsA plus **FK506**. Double mutant **calcineurin** A subunits (Y377F, W388C CMP1 and Y419F, W430C CMP2) confer resistance to CsA, to **FK506** and to CsA plus **FK506** . These studies identify cyclophilin A-CsA and FKBP12-**FK506** binding targets as distinct, highly conserved regions of **calcineurin** A that overlap the binding domain for the **calcineurin** B regulatory subunit.
IT **9025-75-6, Calcineurin**
RL: BPR (Biological process); PRP (Properties); BIOL (Biological study); PROC (Process)
(CMP2 and CMP1 subunit A; targets of immunophilin-immunosuppressant complexes are distinct highly conserved regions of **calcineurin** A)
IT **104987-11-3**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(**calcineurin**-distinct binding site for; targets of immunophilin-immunosuppressant complexes are distinct highly conserved regions of **calcineurin** A)

L117 ANSWER 25 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:629281 HCAPLUS
DN 123:165623
TI Localization of protein phosphatase
AU Ito, Masaaki; Shimizu, Hiroyuki; Nakano, Takeshi
CS Sch. Medicine, Mie Univ., Tsu, 514, Japan
SO Seitai no Kagaku (**1995**), 46(2), 156-61
CODEN: SEKAA6; ISSN: 0370-9531
DT Journal; General Review
LA Japanese
AB A review, with 37 refs., on tissue and subcellular localization, **mol. structures**, and activity regulatory mechanism of serine/threonine protein phosphatases.
IT **9025-75-6**, Protein phosphatase
RL: BAC (Biological activity or effector, except adverse); BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(tissue and subcellular localization, **mol. structures** , and activity regulatory mechanism of serine/threonine protein phosphatases)

L117 ANSWER 26 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:501858 HCAPLUS
DN 122:307598
TI Comparative analysis of mouse NotI linking clones with mouse and human genomic sequences and transcripts
AU Plass, Christoph; Kawai, Jun; Kalcheva, Iveta; Davis, Leslie; Watanabe, Sachihiko; Hayashizaki, Yoshihide; Chapman, Verne
CS Dep. Molecular Cellular Biology, Roswell Park Cancer Inst., Buffalo, NY, 14263-0001, USA
SO DNA Res. (**1995**), 2(1), 27-35
CODEN: DARSE8; ISSN: 1340-2838
DT Journal
LA English
AB NotI cleavage sites are frequently assocd. with CpG islands that identify the 5' regulatory sites of functional genes in the genome. Therefore we analyzed a sample of 22 NotI linking clones prepd. from mouse brain DNA, to det. whether these mouse NotI site assocd. clones could be used for comparative anal. of mouse and human genomes by cross-reaction with both mouse and human genomic DNA and RNA in Southern and Northern hybridization. We further examd. whether we could establish the identity of these clones with known genes by comparing the nucleotide sequences surrounding the NotI site with the GenBank **database**. We obsd. that 70% of the clones cross-hybridized with human DNA and that 4 of 11 tested clones (36%) detected a transcript in human HeLa cells RNA whereas 73% clones (8/11) detected transcripts in mouse RNAs from one or more organs. Single pass sequence anal. was successful on 16 of 19 clones. The GC content in these sequences was very high (48.8% to 73.8%) suggesting that 12 of 16 sequenced clones contained a CpG island. Three out of 19 clones showed significant similarity with previously analyzed mouse gene sequences in GenBank, including the mouse rRNA gene family, cathepsin and the scip POU-domain genes. In addn., two sequences showed significant similarity to the human and rabbit protein phosphatase 2A-.beta. subunit and the human transforming growth factor-.beta.. Thus, 5 of 16 clones showed homol. with identified genes. These results and the recent work of using RLGS methods for genetic mapping indicate that NotI linking clones can be used to efficiently cross ref. a comparative anal. of the mouse and human genomic maps.
IT **9025-75-6**
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(2A, .beta.-subunit; two mouse NotI linking clone sequences showed significant similarity to the human and rabbit protein phosphatase 2A-.beta. subunit and the human transforming growth factor-.beta.)

L117 ANSWER 27 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:388937 HCAPLUS
DN 122:265997
TI CD45 protein tyrosine phosphatase: determination of minimal peptide length for substrate recognition and synthesis of some tyrosine-based electrophiles as potential active-site directed irreversible inhibitors
AU Bobko, Mark; Wolfe, Henry R.; Saha, Ashis; Dolle, Roland E.; Fisher, Diana K.; Higgins, Terry J.
CS Department of Medicinal Chemistry, Sterling Winthrop Pharmaceuticals Research Division, Collegeville, PA, 19426, USA
SO Bioorg. Med. Chem. Lett. (**1995**), 5(4), 353-6
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB Using fyn protein tyrosine kinase as a template, a series of phosphopeptides spanning in length from 1-14 amino acids was prepd. Kinetic evaluation of the series suggest that CD45 does not have a strong preference for its N- or C-terminal amino acids, and that extended phosphopeptides are not required for efficient substrate turnover.

L117 ANSWER 28 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:362789 HCAPLUS

DN 123:26830
TI The sequence of a 13.5 kb DNA segment from the left arm of yeast chromosome XIV reveals MER1; RAP1; a new putative member of the DNA replication complex and a new putative serine/threonine phosphatase gene
AU Coster, Francoise; Van Dyck, Luc; Jonniaux, Jean-Luc; Purnelle, Benedicte Goffeau, Andre
CS Unite Biochimie Physiologique, Universite Catholique Louvain, Louvain-la-Neuve, 1348, Belg.
SO Yeast (**1995**), 11(1), 85-91
CODEN: YESTE3; ISSN: 0749-503X
DT Journal
LA English
AB The nucleotide sequence of two adjacent ClaI fragments from the left arm of Saccharomyces cerevisiae chromosome XIV has been detd. Anal. of the 13,520 bp DNA segment reveals nine open reading frames (ORFs) longer than 300 bp. N1302 contains the consensus sequence for a phosphate-binding loop common to ATP- and GTP-binding proteins and a strictly conserved 'SRC' sequence of unknown function present in all accessory proteins of replicative polymerases. N1306 shares homologies with serine/threonine phosphatases. N1310 encodes RAP1 (TUF or SBF-E), a transcription regulator. N1330 is the MER1 gene required for chromosome pairing and genetic recombination. Two ORFs show no homol. with proteins in the **databases** and no particular features. N1311 is not likely to be expressed as it is located on the complementary strand of N1310. The sequence has been submitted to the EMBL data library under Accession No. X78898.
IT **9025-75-6**, Serine/threonine phosphatase
RL: BSU (Biological study, unclassified); BIOL (Biological study)
(sequence of a 13.5-kb DNA segment from the left arm of yeast chromosome XIV reveals MER1; RAP1; a new putative member of the DNA replication complex and a new putative serine/threonine phosphatase gene)

L117 ANSWER 29 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:357164 HCAPLUS
DN 123:162427
TI 22 Genes from chromosome 17q21: cloning, sequencing, and characterization of mutations in breast cancer families and tumors
AU Friedman, Lori S.; Ostermeyer, Elizabeth A.; Lynch, Eric D.; Welcsh, Piri; Szabo, Csilla I.; Meza, Jose E.; Anderson, Lee A.; Dowd, Patrick; Lee, Ming K.; et al.
CS School Public Health, Univ. California, Berkeley, CA, 94720, USA
SO Genomics (**1995**), 25(1), 256-63
CODEN: GNMCEP; ISSN: 0888-7543
DT Journal
LA English
AB In our effort to identify BRCA1, 22 genes were cloned from a 1-Mb region of chromosome 17q21 defined by meiotic recombinants in families with inherited breast and/or ovarian cancer. Subsequent discovery of another meiotic recombinant narrowed the region to .apprx.650 kb. Genes were cloned from fibroblast and ovarian cDNA libraries by direct screening with YACs and cosmids. The more than 400 cDNA clones so identified were mapped to cosmids, YACs, and P1 clones and to a chromosome 17 somatic panel informative for the BRCA1 region. Clones that mapped back to the region were hybridized to each other and consolidated into clusters reflecting 22 genes. Ten genes were known human genes, 5 were human homologs of known genes, and 7 were novel. Each gene was sequenced, compared to genes in the **databases** to find homologies, and analyzed for mutations in BRCA1-linked families and tumors. Eight mutations were found in tumors or families and not in controls. In the gene encoding .alpha.-N-acetylglucosaminidase, .apprx.100 kb proximal to the 650-kb linked region, somatic nonsense, missense, and splice junction mutations occurred in 3 breast tumors, but not in these patients' germline DNA nor in controls. In an ets-related oncogene in the linked region, a missense mutation cosegregated with breast cancer in one family and was not obsd. in controls. In a human homolog of a yeast pre-mRNA splicing factor, 3

different mutations cosegregated with breast cancer in 3 families and were not obsd. in controls. In these and the other genes in the region, 36 polymorphic variants were obsd. in both cases and controls.

IT **9025-75-6**, Phosphatase, phosphoprotein
RL: BOC (Biological occurrence); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(cloning, sequencing, and characterization of mutations in 22 genes from human chromosome 17q21 in breast cancer families and tumors)

L117 ANSWER 30 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:273498 HCAPLUS
DN 122:45991
TI The molecular replacement solution and **x-ray** refinement to 2.8 .ANG. of a decameric complex of human cyclophilin A with the immunosuppressive drug cyclosporin A
AU Pfluegl, Gaston M.; Kallen, Joerg; Jansonius, Johan N.; Walkinshaw, Malcom D.
CS Dep. Structural Biology, Univ. Basel, Basel, CH-4056, Switz.
SO J. Mol. Biol. (**1994**), 244(4), 385-409
CODEN: JMOBAK; ISSN: 0022-2836
DT Journal
LA English
AB The **x-ray** structure of a decameric form of a complex of human cyclophilin A (CypA) with the immunosuppressive drug cyclosporin A (CsA) has been detd. The **crystals** of space group P4a212 with cell dimensions a = b = 95.2 .ANG., c = 280.0 .ANG. have five copies of the cyclophilin A/cyclosporin A complex in the asym. unit. The structure was solved by mol. replacement techniques, using a known cyclophilin A model. Procedures were developed to construct a self-rotation function using the results of cross-rotation searches. The comparison of exptl. and constructed self-rotation maps was an important aid in selecting the correct rotation function soln. The translation functions revealed the presence of a cyclic pentamer. A **crystallog**. dimer axis passes through the non-**crystallog**. 5-fold rotation axis of the pentameric asym. unit, and generates a decameric "sandwich" of CypA/CsA heterodimers that has 52 symmetry. The five CypA/CsA protomers were refined independently using all data to 2.8 .ANG. giving a final **crystallog**. R-factor of 15.7%. Despite the constraints due to the packing arrangement within the decamer, the CypA and CsA conformations are similar to other CypA/CsA structures detd. by **x-ray** **crystallog**. and NMR spectroscopy. The hydrophobic CsA mols. are embedded in the middle of the decameric sandwich with only 20% of their surface exposed to solvent. The binding loop of CsA (residues 1 to 3 and 9 to 11) comprising 42% of the CsA surface, is buried in the peptidyl-prolyl-cis-trans isomerase active site of the cognate binding partner CypA, while the effector loop (residues 4 to 8) packs in the core of the decamer making hydrogen-bonding and van der Waals contacts with three neighboring mols. The environment of CsA in the decamer has been analyzed and may provide a mimic for the interactions likely to occur between the CypA/CsA complex and its biol. target **calcineurin**. There is no evidence to suggest that the decameric sandwich itself plays a role in immunosuppression by inhibiting **calcineurin**. However, the chaperone/foldase activity of CypA could require oligomer formation for its biol. function.

L117 ANSWER 31 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:30679 HCAPLUS
DN 122:179669
TI The identification of novel gene sequences of the human adult testis
AU Affara, Nabeel A.; Bentley, Elizabeth; Davey, Phillip; Pelmear, Adele; Jones, Michael H.
CS Dep. Pathol., Univ. Cambridge, Cambridge, CB2 1QP, UK
SO Genomics (**1994**), 22(1), 205-10
CODEN: GNMCEP; ISSN: 0888-7543
DT Journal
LA English

AB The facilitate the characterization of genetic expression in human adult testis, expressed sequence tag anal. of cDNAs from this tissue has been undertaken. Over 180 kb of DNA sequence has been detd. and used to search the GenBank **database**. The results from the first 359 cDNA clones analyzed indicate that the sequences could be sorted into several categories with a high proportion being novel. Twenty-five clones (7%) showed 100% identity with human genes, 11 (3%) with prokaryotic sequences, 21 (5%) with between 60 and 95% similarity to human genes, 27 (8%) with between 60 and 95% similarity to genes from other species, and 33 (%) with matches to human repeat sequences. Two hundred forty-two (67%) showed no significant matches and thus are likely to represent novel transcripts. In comparison to similar studies on human brain tissue and a hepatoma cell line, the findings indicate that the matches in the testis transcript population appear to be identifying a different spectrum of gene sequence.

IT **9025-75-6**, Protein phosphatase
RL: BOC (Biological occurrence); BSU (Biological study, unclassified); PRP (Properties); BIOL (Biological study); OCCU (Occurrence)
(2C .alpha., EST for; identification of novel gene sequences of human adult testis)

L117 ANSWER 32 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1995:15378 HCAPLUS
DN 122:99786
TI Regulation of Shaker K+ channel inactivation gating by the cAMP-dependent protein kinase
AU Drain, Peter; Dubin, Adrienne E.; Aldrich, Richard W.
CS Sch. Med., Stanford Univ., Stanford, CA, 94305, USA
SO Neuron (**1994**), 12(5), 1097-109
CODEN: NERNET; ISSN: 0896-6273
DT Journal
LA English
AB In response to depolarization of the membrane potential, Shaker K+ channels undergo a series of voltage-dependent conformational changes, from resting to open conformations followed by a rapid transition into a long-lived closed conformation, the N-type inactivated state. Application of phosphatases to the cytoplasmic side of Shaker channels in excised inside-out patches slows N-type inactivation gating. Subsequent application of the purified catalytic subunit of the cAMP-dependent protein kinase (PKA) and ATP reverses the effect, accelerating N-type inactivation back to its initial rapid rate. Macroscopic and single-channel expts. indicate that N-type inactivation is selectively modulated. There was little or no effect on the voltage dependence and kinetics of activation. Comparison of site-directed mutant channels shows that a C-terminal consensus site for PKA phosphorylation is responsible for the modulation. Since a cell's integrative characteristics can be detd. by the rate of inactivation of its voltage-dependent channels, modulation of these rates by phosphorylation is likely to have functional consequences.

IT **9025-75-6**
RL: BAC (Biological activity or effector, except adverse); BIOL (Biological study)
(slowing of N-type inactivation gating by; Shaker K+ channel N-type inactivation gating regulation by cAMP-dependent protein kinase)

L117 ANSWER 33 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:678831 HCAPLUS
DN 121:278831
TI The latch region of **calcineurin** B is involved in both immunosuppressant-immunophilin complex docking and phosphatase activation
AU Milan, David; **Griffith, Jim**; Su, Michael; Price, E. Roydon; McKeon, Frank
CS Dep. Cell. Biol., Harvard Med. Sch., Boston, MA, 02115, USA
SO Cell (Cambridge, Mass.) (**1994**), 79(3), 437-47
CODEN: CELLB5; ISSN: 0092-8674
DT Journal
LA English

AB The immunosuppressants cyclosporin A and **FK506**, when complexed with their intracellular receptors, prevent T cell activation by directly binding to the phosphatase **calcineurin**. The authors have used **mol. modeling** and mutagenesis to identify sites on **calcineurin** important for this interaction. They have created **calcineurins** that are resistant to both cyclosporin A and **FK506** by mutating specific residues in **CnB**, a calcium-binding protein that regulates the catalytic subunit, **CnA**. Significantly, on a model of **CnB**, these mutations map to the latch region, an element of tertiary **structure** that forms when **CnB** binds **CnA**. In addn., this latch region plays an important role in activating the catalytic subunit **CnA**. These results suggest a mol. mechanism for suppression of **calcineurin** by cyclosporin A and **FK506** involving their binding to the same region of **CnB** used for allosterically activating **CnA**.

IT **104987-11-3, Fk506**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(latch region of **calcineurin** B involved in immunosuppressant-immunophilin complex docking and phosphatase activation)

IT **9025-75-6**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(subunit B; latch region of **calcineurin** B involved in immunosuppressant-immunophilin complex docking and phosphatase activation)

L117 ANSWER 34 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:671613 HCAPLUS
DN 121:271613
TI Solution **Structure** of **FK506** Bound to the R42K, H87V Double Mutant of **FKBP-12**
AU Lepre, Christopher A.; Pearlman, David A.; Cheng, Jya-Wei; DeCenzo, Maureen T.; Moore, Jonathan M.; Livingston, David J.
CS Vertex Pharmaceuticals Incorporated, Cambridge, MA, 02139-4211, USA
SO Biochemistry (**1994**), 33(46), 13571-80
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB The binding of the **FK506/FKBP-12** complex to **calcineurin** (CN), its putative target for immunosuppression, involves recognition of solvent-exposed regions of the ligand as well as **FKBP-12** residues near the active site. The R42K, H87V double mutation of **FKBP-12** decreases the CN affinity of the complex by 550-fold [Aldape, R. A., Futer, O., DeCenzo, M. T., Jarrett, B. P., Murcko, M. A., & Livingston, D. J. (1992) J. Biol. Chem., 267, 16029-16032]. This work reports the soln. **structure** of 13C-labeled **FK506** bound to R42K, H87V **FKBP-12**. Assignments and nuclear Overhauser effect (NOE) measurements at three mixing times were made from inverse-detected 1H-13C NMR expts. **Structures** were calcd. by several different methods, including distance geometry, restrained **mol.** dynamics, and **mol.** dynamics with time-averaged restraints. The NMR **structures** of the ligand are very well defined by the NOE restraints and differ slightly from the **x-ray structure** in regions that are involved in **crystal** packing. Comparison with the NMR **structure** of **FK506** bound to wild-type **FKBP-12** reveals that the R42K, H87V mutation causes the ligand backbone near C16 to move by 2.5 to 4.5 .ANG., reorients 15-MeO by 90.degree., and shifts 13-MeO by approx. 1.5 .ANG.. **FK506** appears to undergo a concerted, mutationally induced shift in the binding pocket, with the greatest changes occurring in the effector region of the drug. The altered effector **conformation** of mutant-bound **FK506** may perturb interactions between the drug and CN, thus accounting for the effect of the double mutation upon the CN inhibitory activity of the

complex.
IT **9025-75-6, Calcineurin**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(binding; soln. **structure** of **FK506** bound to R42K H87V double mutant of **FKBP-12**)
IT **104987-11-3D, FK506, FKBP-12**
complexes
RL: BAC (Biological activity or effector, except adverse); PRP (Properties); BIOL (Biological study)
(soln. **structure** of **FK506** bound to R42K H87V double mutant of **FKBP-12**)

L117 ANSWER 35 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:652318 HCAPLUS
DN 121:252318
TI Local communication within dendritic spines: models of second messenger diffusion in granule cell spines of the mammalian olfactory bulb
AU Woolf, Thomas B.; Greer, Charles A.
CS Sch. Med., Yale Univ., New Haven, CT, 06510, USA
SO Synapse (N. Y.) (**1994**), 17(4), 247-67
CODEN: SYNAET; ISSN: 0887-4476
DT Journal
LA English
AB Dendritic spines are generally believed to play a role in modulating synaptically induced elec. events. In addn., they may also confine second messengers and thus topol. limit the distance over which second messenger cascades may be functionally significant. To address this possibility, **computer** simulations of transient second messenger concn. changes were performed. The results show the importance of spine morphol. and binding and extrusion mechanisms in controlling second messenger transients. In the presence of intrinsic cytoplasmic binding sites and kinetic rates similar to that expected for calcium, second messengers were confined to the spine head. In the absence of binding/extrusion mechanisms, the size and time course of the input transient to the spine head influenced the second messenger transients that might be seen at the base of the spine neck and in other spines. Large and/or sustained increases in second messenger concn. in the spine head were communicated to the spine base and to other spine heads. The results emphasize the importance of a knowledge of breakdown pathways, concns. and kinetics of binding sites, and extrusion mechanisms for understanding the dynamics of local chem. changes for dendritic spine function.
IT **9025-75-6, Calcineurin**
RL: PRP (Properties)
(second messenger diffusion modeling for olfactory bulb spines)

L117 ANSWER 36 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:647647 HCAPLUS
DN 121:247647
TI Prevalence and distribution of introns in non-ribosomal protein genes of yeast
AU Rodriguez-Medina, Jose R.; Rymond, Brian C.
CS Dep. Biochem., Univ. Puerto Rico, San Juan, 365067, P. R.
SO Mol. Gen. Genet. (**1994**), 243(5), 532-539
CODEN: MGGEAE; ISSN: 0026-8925
DT Journal
LA English
AB Relatively few genes in the yeast Saccharomyces cerevisiae are known to contain intervening sequences. As a group, yeast ribosomal protein genes exhibit a higher prevalence of introns when compared to non-ribosomal protein genes. In an effort to quantify this bias we have estd. the prevalence of intron sequences among non-ribosomal protein genes by assessing the no. of prp2-sensitive mRNAs in an in-vitro translation assay. These results, combined with an updated survey of the GenBank DNA **database**, support an est. of 2.5% for intron-contg. non-ribosomal protein genes. Furthermore, our observations reveal an intriguing distinction between the distributions of ribosomal protein and

non-ribosomal protein intron lengths, suggestive of distinct, gene class-specific evolutionary pressures.

IT **144517-47-5**, Genbank M87508-derived protein
RL: PRP (Properties)
(prevalence and distribution of introns in non-ribosomal protein genes of yeast)

L117 ANSWER 37 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:624962 HCAPLUS
DN 121:224962
TI Mutational analysis of a Ser/Thr phosphatase. Identification of residues important in phosphoesterase substrate binding and catalysis
AU Zhuo, Shoqiu; Clemens, James C.; Stone, Randy L.; Dixon, Jack E.
CS Dep. Biol. Chem., Univ. Michigan, Ann Arbor, MI, 48109, USA
SO J. Biol. Chem. (**1994**), 269(42), 26234-8
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The SEr/Thr **phosphoprotein phosphatases** (PPases) display similarities in amino acid sequence and biochem. properties. Most members of this family require transition metal ions for activity. The smallest family member, the bacteriophage .lambda. PPase (.lambda.-PPase), has been successfully overexpressed in Escherichia coli, purified, and characterized (Zhuo, S., et al., 1993). Site-directed mutagenesis has now been employed to define amino acid residues in .lambda.-PPase required for metal ion binding and catalysis. Conservative amino acid substitutions at residues Asp20, Hsp22, Asp49, His76, and Glu717 affected .lambda.-PPase catalysis and metal ion binding, whereas substitutions at residues Arg53 and Arg73 affected catalysis and substrate binding. Each of these residues is invariant in all **phosphoprotein phosphatases**, suggesting that these residues may play important roles in binding and catalysis in all of the PPases. **Computer**-assisted sequence alignment further revealed that .lambda.-PPase residues Asp20, His22, Asp49, His76, Arg53, and Arg73 lie within three larger regions of PPase sequence identity with the consensus sequence (DXH-(.apprx.25)-GDXXD-(.apprx.25)-GNHD/E). This motif can be found in a wide variety of phosphoesterases unrelated to the PPases and defines structural and catalytic features utilized by a diverse group of enzymes for the hydrolysis of phosphate esters.

IT **9025-75-6**, Serine/threonine **phosphoprotein phosphatase**
RL: ANT (Analyte); ANST (Analytical study)
(mutational anal. of a ser/thr phosphatase from .lambda. phage - identification of residues important in phosphoesterase substrate binding and catalysis)

L117 ANSWER 38 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:624619 HCAPLUS
DN 121:224619
TI The molecular basis of receptor-ligand-receptor interactions: studies of the immunophilin FKBP12
AU Rosen, Michael Keith
CS Harvard Univ., Cambridge, MA, USA
SO (**1993**) 326 pp. Avail.: Univ. Microfilms Int., Order No. DA9412390
From: Diss. Abstr. Int. B, 1994, 54(11), 5675
DT Dissertation
LA English
AB Unavailable

IT **9025-75-6, Calcineurin**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(inhibition by immunophilins of; the mol. basis of receptor-ligand-receptor interactions: studies of the immunophilin FKBP12)

IT **104987-11-3, FK506**
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(interaction with FKBP-12 of; the mol. basis of receptor-ligand-

receptor interactions: studies of the immunophilin FKBP12)

L117 ANSWER 39 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:622344 HCAPLUS
DN 121:222344
TI Stimulation of androgen-regulated transactivation by modulators of protein phosphorylation
AU Ikonen, Tarja; Palvimo, Jorma J.; Kallio, Pekka J.; Reinikainen, Piia; Janne, Olli A.
CS Inst. Biomedicine, Univ. Helsinki, Helsinki, Finland
SO Endocrinology (**1994**), 135(4), 1359-66
CODEN: ENDOAO; ISSN: 0013-7227
DT Journal
LA English
AB The effect of modulators of protein phosphorylation on the transcriptional activity of the androgen receptor (AR) was studied under transient expression conditions. Activators of protein kinase-A (8-bromo-cAMP) and protein kinase-C (phorbol 12-myristate 13-acetate) or an inhibitor of protein phosphatase-1 and -2A (okadaic acid) influenced minimally pMMTV-chloramphenicol acetyltransferase (CAT) activity in CV-1 cells cotransfected with an AR expression plasmid in the absence of androgen. In the presence of testosterone, however, all compds. enhanced AR-mediated transactivation by 2-4-fold. A nonsteroidal antiandrogen, Casodex, behaved as a pure antagonist; it blunted the action of testosterone and was not rendered agonistic by activators of protein kinase-A. A reporter plasmid contg. two androgen response elements (AREs) in front of the thymidine kinase promoter (pARE2tk-CAT) was also used to examine promoter specificity. It was activated by 8-Br-cAMP, forskolin, or okadaic acid even without AR or androgen. However, when forskolin or okadaic acid was used together with androgen and AR, the resulting AR-dependent transactivation of pARE2tk-CAT was more than additive. Intact DNA- and ligand-binding domains, but not the N-terminal amino acid residues 40-147, of the receptor were mandatory for the synergism between protein kinase-A activators and androgen. Immunoreactive AR content in transfected COS-1 cells was not influenced by exposure to 8-Br-cAMP. Similar results were obtained by ligand binding assays. Quant. or qual. differences were not obsd. in DNA-binding characteristics between receptors extd. from cells treated with testosterone with or without protein kinase-A activator. Collectively, the synergistic stimulation of AR-dependent transactivation by androgen and protein kinase activators is not due to changes in cellular AR content or affinity of the receptor for the cognate DNA element; rather, this phenomenon seems to result from altered interaction of ligand-activated AR with other proteins in the transcription machinery.
IT **9025-75-6**, Protein phosphatase
RL: BPR (Biological process); BIOL (Biological study); PROC (Process)
(androgen-regulated transactivation modulation by protein phosphorylation)

L117 ANSWER 40 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:602360 HCAPLUS
DN 121:202360
TI The redox active components H2O2 and N-acetyl-L-cysteine regulate expression of c-jun and c-fos in lens systems
AU Li, Wan-Cheng; Wang, Guo-Ming; Wang, Ren-Rong; Spector, Abraham
CS College Physicians Surgeons, Columbia University, New York, NY, 10032, USA
SO Exp. Eye Res. (**1994**), 59(2), 179-90
CODEN: EXERA6; ISSN: 0014-4835
DT Journal
LA English
AB Hydrogen peroxide (H2O2) is implicated in human cataract development. At the mol. level H2O2 has been obsd. to cause damage to DNA, protein and lipid. It is now demonstrated, for the first time in a lens system, that H2O2 at concns. found in cataract patients induces expression of both c-jun and c-fos. At optimal concns. of H2O2, mRNA accumulation of c-jun and c-fos in the rat lenses is induced 20- and 18-fold above normal levels resp., but with distinct kinetics. This induction occurs at the

transcriptional level. H2O2 also induces transactivation by activating protein-1 (AP-1) in c-jun and c-fos. Preincubation of rat lenses with 5 mM NAC inhibits the induction by H2O2, while 30 mM and 50 mM NAC induce expression of these genes and mask the H2O2 effect. H7 (50 .mu.M), genistein (2 .mu.M) and okadaic acid (20 nM), all block the induction of c-jun and c-fos mRNA accumulation in the H2O2-treated rat lenses. These results suggest that H2O activates protein kinase and phosphatase dependent signal transduction pathways to induce c-jun and c-fos expression which may regulate lens **cryst**. genes and other genes contg. AP-1 binding sites.

IT **9025-75-6, Phosphoprotein phosphatase**
RL: BAC (Biological activity or effector, except adverse); BPR (Biological process); BIOL (Biological study); PROC (Process)
(signal-transducing; hydrogen peroxide and acetylcysteine effect on expression of c-jun and c-fos in eye lens in relation to cataracts)

L117 ANSWER 41 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:502946 HCAPLUS
DN 121:102946
TI **Crystallization** and preliminary **x-ray** analysis of the low molecular weight phosphotyrosyl protein phosphatase from bovine heart
AU Zhang, Marie; Van Etten, Robert L.; Lawrence, Charles M.; Stauffacher, Cynthia V.
CS Dep. Chem., Purdue Univ., West Lafayette, IN, 47907, USA
SO J. Mol. Biol. (**1994**), 238(2), 281-3
CODEN: JMOBAK; ISSN: 0022-2836
DT Journal
LA English
AB Two **crystal** forms of bovine heart phosphotyrosyl protein phosphatase (BHPTP) have been examd. by **x-ray** anal. One **crystal** form grows as long rods with triclinic **crystal** symmetry and diffracts to 3 .ANG. resoln. The diffraction pattern of this form of the **crystal** shows twinning about a major axis. A second **crystal** form of BHPTP grows as flat trapezoidal prisms with monoclinic symmetry C2, and unit cell parameters a = 95.3 .ANG., b = 43.3 .ANG., c = 41.2 .ANG. and .beta. = 113.5.degree.. The unit cell dimensions indicate that there is one 18 kDa mol. per asym. unit. These **crystals** diffract to at least 2.2 .ANG. resoln. and are resistant to decay in the **x-ray** beam.

L117 ANSWER 42 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:476564 HCAPLUS
DN 121:76564
TI **X-ray structure** of a cyclophilin B/cyclosporin complex: comparison with cyclophilin A and delineation of its **calcineurin**-binding domain
AU Mikol, Vincent; Kallen, Joerge; Walkinshaw, Malcolm D.
CS Sandoz AG, Basel, CH-4002, Switz.
SO Proc. Natl. Acad. Sci. U. S. A. (**1994**), 91(11), 5183-6
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB The **crystal structure** of a complex between recombinant human cyclophilin B (CypB) and a cyclosporin A (CsA) analog has been detd. and refined at 1.85-.ANG. resoln. to a **crystallog**. R factor of 16.0%. The overall **structures** of CypB and of cyclophilin A (CypA) are similar; however, significant differences occur in two loops and at the N and C termini. The CsA-binding pocket in CypB has the same **structure** as in CypA and cyclosporin shows a similar bound **conformation** and network of interactions in both CypB and CypA complexes. The network of the water-mediated contacts is also essentially conserved. The higher potency of the CypB/CsA complex vs. CypA/CsA in inhibiting the Ca2+- and calmodulin-dependent protein phosphatase **calcineurin** is discussed in terms of the structural differences between the two complexes. The three residues Arg90, Lys113, and Ala128

and the loop contg. Arg158 on the surface of CypB are likely to modulate the differences in **calcineurin** inhibition between CypA and CypB.

IT **9025-75-6, Calcineurin**
RL: PROC (Process)
(inhibition of, by cyclophilin B complexes with cyclosporin A, cyclophilin A in relation to)

L117 ANSWER 43 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:449752 HCAPLUS
DN 121:49752
TI Activation mechanisms of **calcineurin** and action mechanisms of immunosuppressive agent (**FK506**)
AU Mukai, Hideyuki
CS Sch. Med., Kobe Univ., Kobe, 650, Japan
SO Kobe Daigaku Igakubu Kiyo (**1993**), 54(1), 25-32
CODEN: KDIKAX; ISSN: 0075-6431
DT Journal
LA Japanese
AB The calmodulin (CLM) antagonists calmidazolium (CLMDZ), trifluoperazine, thioridazine, and W-7 inhibited the Ni2+-stimulated phosphatase (Pase) activity against p-nitrophenyl phosphate and against peptide fragment contg. phosphorylation site of RII subunit of cAMP-dependent protein kinase dose-dependently in the absence of CLM. CLMDZ inhibited the Ni2+-stimulated CLM-independent Pase activity to much the same extent as it did the Ca2+/CLM-stimulated activity. With the addn. of a small amt. of the purified B subunit of **calcineurin** (CLCN), the Ni2+-stimulated Pase activity recovered in the presence of CLMDZ. On the other hand, CLMDZ only weakly and partially inhibited the Mn2+-stimulated Pase activity and the other CLM antagonists examd. increased the Mn2+-stimulated activity, in the absence of CLM. These results indicate that the activation mechanism differs between Ni2+- and Mn2+ stimulation of CLCN, and that the B subunit plays a crucial role in the expression of the Ni2+-stimulated Pase activity. The immunosuppressive agent **FK506** and its 12 KDa isoform binding protein (FKBP12) complex inhibited potently the Ca2+/CLM-stimulated Pase activity of CLCN. On the other hand, **FK506**-FKBP12 complex relatively weakly inhibited the Ni2+- and Mn2+-stimulated, and trypsin-treated divalent metal ion-independent Pase activity of the enzyme. These results suggest that **FK506**-FKBP12 complex has higher affinity of Ca2+/CLM-stimulated **conformational** change, and that the activation mechanism also differs between Ca2+/CLM-stimulation and Ni2+- and Mn2+-stimulation, or trypsin treatment of the enzyme.

IT **9025-75-6, Calcineurin**
RL: BIOL (Biological study)
(a)

IT **104987-11-3, FK506**
RL: BIOL (Biological study)
(calcium/calmodulin-stimulated **calcineurin** response to)

L117 ANSWER 44 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:449599 HCAPLUS
DN 121:49599
TI **Calcineurin** has a very tight-binding pocket for the side chain of residue 4 of cyclosporin
AU Papageorgiou, Christos; Borer, Xaver; French, Richard R.
CS Preclin. Res., Sandoz Pharma Ltd., Basle, CH-4002, Switz.
SO Bioorg. Med. Chem. Lett. (**1994**), 4(2), 267-72
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB Derivs. of cyclosporin A (CsA) at position 4 were synthesized to probe the interaction of the CsA/CypA complex with **calcineurin** (CaN). Both lipophilic and hydrophilic substituents are detrimental for the immunosuppressive activity, indicating that CaN has a very "tight-binding pocket" for this region.

IT **9025-75-6, Calcineurin**

RL: PRP (Properties)
(interaction of, with cyclophilin A-cyclosporin A deriv. complex, immunosuppressive activity and structure in relation to)

L117 ANSWER 45 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:315428 HCAPLUS
DN 120:315428
TI **Crystal** structures of cyclophilin A complexed with cyclosporin A and N-methyl-4-[(E)-2-butenyl]-4,4-dimethylthreonine cyclosporin A
AU Ke, Hengming; Mayrose, Dale; Belshaw, Peter J.; Alberg, David G.; Schreiber, Stuart L.; Chang, Zhi Yuh; Etzkorn, Felicia A.; Ho, Susanna; Walsh, Christopher T.
CS Sch. Med., Univ. North Carolina, Chapel Hill, NC, 27599, USA
SO Structure (London) (**1994**), 2(1), 33-44
CODEN: STRUE6
DT Journal
LA English
AB Cyclophilin (CyP) is a ubiquitous intracellular protein that binds the immunosuppressive drug cyclosporin A (CsA). CyP-CsA forms a ternary complex with **calcineurin** and thereby inhibits T-cell activation. CyP also has enzymic activity, catalyzing the cis-trans isomerization of peptidyl-prolyl amide bonds. Results: The authors have detd. the structure of human cyclophilin A (CyPA) complexed with CsA to 2.1 A resoln. The authors also report here the structure of CyPA complexed with an analog of CsA, N-methyl-4-[(E)-2-butenyl]-4,4-dimethylthreonine CsA (MeBm2t1-CsA), which binds less well to CyPA, but has increased immunosuppressive activity. Comparison of these structures with previously detd. structures of unligated CyPA and CyPA complexed with a candidate substrate for the isomerase activity, the dipeptide AlaPro, reveals that subtle conformational changes occur in both CsA and CyPA on complex formation. MeBm2t1-CsA binds to CyPA in an essentially similar manner to CsA. The 100-fold weaker affinity of its binding may be attributable to the close contact between MeBmt1 and the active site residue Ala103 of CyPA, which causes small conformational changes in both protein and drug. One change, the slight movement of MeLeu6 in CsA relative to MeBm2t1-CsA, may be at least partially responsible for the higher affinity of the CyPA-MeBm2t1-CsA complex for **calcineurin**. The authors' comparison between CyPA-CsA and CyPA-AlaPro suggests that CsA is probably not an analog of the natural substrate, confirming that the catalytic activity of CyPA is not related to its role in immunosuppression either structurally or functionally.

L117 ANSWER 46 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:314968 HCAPLUS
DN 120:314968
TI Cyclosporins: structure-activity relationships
AU Fliri, Hans; Baumann, Goetz; Enz, Albert; Kallen, Juerg; Luyten, Marcel; Mikol, Vincent; Movva, Rao; Quesniaux, Valerie; Schreier, Max; et al.
CS Preclin. Res. Lab., Sandoz Pharma AG, Basel, CH-4002, Switz.
SO Ann. N. Y. Acad. Sci. (**1993**), 696(Immunosuppressive and Antiinflammatory Drugs), 47-53
CODEN: ANYAA9; ISSN: 0077-8923
DT Journal; General Review
LA English
AB A review with 30 refs. Cyclosporin A (Sandimmun) achieves immunosuppressive activity by complex formation with cyclophilin and subsequent binding of the binary complex to and inhibiting protein phosphatase 2B (**calcineurin**). Complexes of nonimmunosuppressive cyclophilin binding cyclosporin analogs do not inhibit protein phosphatase 2B, suggesting a crucial role for this enzyme in T cell activation. Binding of cyclosporin A to cyclophilins A, B, and C, resp., results in complexes of significantly different inhibitory potency. The cyclosporin mol. thus has two functional domains, one mediating cyclophilin binding and a second one endowing affinity of the complex to **calcineurin** , thereby inhibiting its enzyme activity. Structure-activity studies and **x-ray crystallog**. of cyclosporin-cyclophilin

complexes indicate a crucial role of leucine side chains in positions 4 and 6 of the cyclosporin macrocycle for the **calcineurin** interaction.

L117 ANSWER 47 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:293070 HCAPLUS
DN 120:293070
TI Enhancement of **x-ray** cell killing in cultured mammalian cells by the protein phosphatase inhibitor calyculin A
AU Nakamura, Katsumasa; Antoku, Shigetoshi
CS Fac. Med., Kyushu Univ., Fukuoka, 812, Japan
SO Cancer Res. (**1994**), 54(8), 2088-90
CODEN: CNREA8; ISSN: 0008-5472
DT Journal
LA English
AB Effects of calyculin A, a potent inhibitor of protein phosphatases 1 and 2A, on **x-ray** cell killing and chromatin structure were studied using cultured mammalian cells (BHK21). Calyculin A at concns. of 2.5-20 nM enhanced **x-ray** cell killing when exponentially growing BHK21 cells were treated with calyculin A for 30 min after x-irradn. A 30-min treatment with this drug induced chromatin condensation transiently. These results suggest that the enhancement of **x-ray** cell killing by calyculin A is caused by the events assocd. with chromatin condensation. Protein phosphatase-targeting drugs may represent a new class of radiation sensitizers.
IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(inhibition of, **x-ray**-induced cell killing enhancement by)

L117 ANSWER 48 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:238613 HCAPLUS
DN 120:238613
TI 15N NMR Relaxation Studies of the **FK506** Binding Protein: Dynamic Effects of Ligand Binding and Implications for **Calcineurin** Recognition
AU Cheng, Jya-Wei; Lepre, Christopher A.; Moore, Jonathan M.
CS Vertex Pharmaceuticals Incorporated, Cambridge, MA, 02139-4211, USA
SO Biochemistry (**1994**), 33(14), 4093-100
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB Backbone dynamics of the ligand- (**FK506**-) bound protein FKBP-12 (107 amino acids), have been examd. using 15N relaxation data derived from inverse-detected two-dimensional 1H-15N NMR spectra. A model free formalism (Lipari & Szabo, 1982) was used to derive the generalized order parameter (S2), the effective correlation time for internal motions (.tau.e), and the chem.-exchange line width (Rex)based on the measured 15N relaxation rate consts. (R1, R2) and 1H-15N heteronuclear NOEs. The final optimized overall correlation time (.tau.m) was 9.0 ns. The av. order parameter (S2) describing the amplitude of motions on the picosecond time scale was found to be 0.88, indicating that internal flexibility is restricted along the entire polypeptide chain. In contrast to results obtained for uncomplexed FKBP, the 80's loop (residues 82-87) surrounding the ligand binding site was found to be rigidly fixed, indicating that internal motions at this site are damped significantly due to stabilizing noncovalent interactions with the **FK506** mol. Structural implications of these differences in picosecond mobility as well as possible implications for **calcineurin** recognition are discussed.
IT **104987-11-3**, **FK506**
RL: BIOL (Biological study)
(FKBP-12 protein binding by, internal flexibility response to, **calcineurin** recognition in relation to)
IT **9025-75-6**, **Calcineurin**
RL: BIOL (Biological study)
(FKBP-12 protein recognition of, ligand binding effect on protein

internal flexibility in relation to)

L117 ANSWER 49 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:235689 HCAPLUS
DN 120:235689
TI Atomic **Structure** of the Immunophilin FKBP13-**FK506** Complex: insights into the Composite Binding Surface for **Calcineurin**
AU Schultz, L. Wayne; Martin, Patrick K.; Liang, Jun; Schreiber, Stuart L.; Clardy, Jon
CS Dep. Chem., Cornell Univ., Ithaca, NY, 14853-1301, USA
SO J. Am. Chem. Soc. (**1994**), 116(7), 3129-30
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
AB The authors detd. the **three-dimensional structure** of FKBP13-**FK506** by high-resoln. (2.0 .ANG.) **x-ray** diffraction techniques to define the architecture of FKBP13 and to identify, through a comparison of FKBP13-**FK506** with **FKBP12-FK506**, prominent features of the composite binding surface.
IT **9025-75-6, Calcineurin**
RL: BIOL (Biological study)
(**crystal structure** of FKBP13-**FK 506** complexes in relation to binding for)
IT **104987-11-3D, FK506**, FKBP13 protein complexes
RL: PRP (Properties)
(**crystal structure** of, **calcineurin** binding in relation to)

L117 ANSWER 50 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:212978 HCAPLUS
DN 120:212978
TI Isopalinurin: a mild protein phosphatase inhibitor from a southern Australian marine sponge, Dysidea sp. [Erratum to document cited in CA120(9):102473v]
AU Murray, Leanne; Sim, Alistair T. R.; Mudge, Lisa-Maree; Rostas, John A. P.; Capon, Robert J.
CS Sch. Chem., Univ. Melbourne, Parkville, 3052, Australia
SO Aust. J. Chem. (**1993**), 46(11), 1824
CODEN: AJCHAS; ISSN: 0004-9425
DT Journal
LA English
AB The errors were not reflected in the abstr. or the index entries.
IT **9025-75-6**
RL: PROC (Process)
(inhibition of, by sesterterpene of southern Australian marine sponge (Erratum))

L117 ANSWER 51 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:211388 HCAPLUS
DN 120:211388
TI Proton, carbon-13, nitrogen-15 nuclear magnetic resonance backbone assignments and secondary structure of human **calcineurin** B
AU Anglister, Jacob; Grzesiek, Stephan; Wang, Andy C.; Ren, Hao; Klee, Claude B.; Bax, Ad
CS Lab. Chem. Phys., Natl. Inst. Diabetes Dig. Kidney Dis., Bethesda, MD, 20892, USA
SO Biochemistry (**1994**), 33(12), 3540-7
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB The calmodulin- and calcium-stimulated protein phosphatase **calcineurin**, PP2B, consists of two subunits: **calcineurin** B, which binds Ca2+, and **calcineurin** A, which contains the catalytic site and a calmodulin binding site. Heteronuclear **3D**

and 4D NMR expts. were carried out on a recombinant human **calcineurin** B which is a 170-residue protein of mol. mass 19.3 kDa, uniformly labeled with 15N and 13C. The nondenaturing detergent CHAPS was used to obtain a monomeric form of **calcineurin** B. **Three-dimensional** triple resonance expts. yielded complete sequential assignment of the backbone nuclei (1H, 13C, and 15N). This assignment was verified by a 4D HN(COCA)NH expt. carried out with 50% randomly deuterated and uniformly 15N- and 13C-enriched **calcineurin** B. The secondary structure of **calcineurin** B has been detd. on the basis of the 13C.alpha. and 13C.beta. secondary chem. shifts, J(HNH.alpha.) couplings, and NOE connectivities obtained from **3D** 15N-sepd. NOESY and 4D 13C/15N-sepd. NOESY spectra. **Calcineurin** B has eight helixes distributed in four EF-hand, helix-loop-helix [Kretsinger, R. H. (1980) CRC Crit. Rev. Biochem. 8, 119-174] calcium binding domains. The secondary structure of **calcineurin** B is highly homologous to that of calmodulin. In comparison to calmodulin, helixes B and C are shorter while helix G is considerably longer. As was obsd. for calmodulin in soln., **calcineurin** B does not have a single long central helix; rather, helixes D and E are sepd. by a six-residue sequence in a flexible nonhelical conformation.

IT **9025-75-6, Calcineurin**
RL: BIOL (Biological study)
(B, secondary structure of, of human, NMR study of, calmodulin in relation to)

L117 ANSWER 52 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:210493 HCAPLUS
DN 120:210493
TI Affinity of okadaic acid to type-1 and type-2A protein phosphatases is markedly reduced by oxidation of its 27-hydroxyl group
AU Sasaki, Katsunori; Murata, Michio; Yasumoto, Takeshi; Mieskes, Gottfried; Takai, Akira
CS Fac. Agric., Tohoku Univ., Sendai, Japan
SO Biochem. J. (**1994**), 298(2), 259-62
CODEN: BIJOAK; ISSN: 0306-3275
DT Journal
LA English
AB Okadaic acid (OA), a potent inhibitor of type-1 and type-2A protein phosphatases (PP1 and PP2A), has four hydroxyl groups at 2, 7, 24 and 27 positions. By chem. treatment of OA the authors synthesized a deriv., in which the 27-hydroxyl group was specifically oxidized (27-dehydro-OA). The inhibitory effect of this OA deriv. was examd. on the activities of PP1 and PP2A, which were inhibited by intact OA with dissocn. consts. (Ki) of 150 nM and 32 pM resp. The authors found that the affinity of OA was decreased 40-fold (Ki = 6 .mu.M) with PP1 and 230-fold (Ki = 7.3 nM) with PP2A after oxidn. of the 27-hydroxyl group. According to the model of the **three-dimensional conformation** of OA on the basis of **x-ray** analyses, the 27-hydroxyl group appears to be present in a position relatively free from intramol. bonding formation, in comparison with the other three hydroxyl groups. The marked increases in the Ki values for PP1 and PP2A, which indicate the redn. of the abs. values of the free energy of binding by 9 kJ/mol and 14 kJ/mol resp., may imply that the 27-hydroxyl group serves as a binding site with the phosphatase mols.

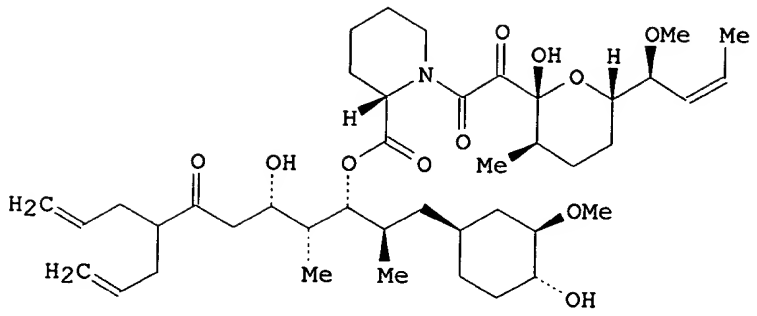
IT **9025-75-6**, Protein phosphatase 1
RL: BIOL (Biological study)
(1 and 2A, of muscle, okadate and derivs. effect on)

L117 ANSWER 53 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:186054 HCAPLUS
DN 120:186054
TI Co-**crystallization** of the catalytic subunit of the serine/threonine specific protein phosphatase 1 from human in complex with microcystin LR
AU Barford, David; Keller, James C.

CS W. M. Keck Struct. Biol. Lab., Cold Spring Harbor Lab., Cold Spring Harbor, NY, 11724, USA
SO J. Mol. Biol. (**1994**), 235(2), 763-6
CODEN: JMOBAK; ISSN: 0022-2836
DT Journal
LA English
AB The catalytic subunit of the serine/threonine specific protein phosphatase 1 from human (mol. mass 37 KDa) has been co-**crystd**. in complex with the cyanobacterial toxin microcystin LR (mol. mass 1 kDa). The **crystals** diffract to a resoln. of 2.8 .ANG. when exposed to synchrotron radiation and belong to space group P21212 with a = 109.5 .ANG., b = 90.6 .ANG., c = 38.7 .ANG.. There is one mol. of protein phosphatase 1 per asym. unit. The **crystal** form is suitable for the detn. of the at. structure of protein phosphatase 1.
IT **9025-75-6D**, Protein phosphatase 1, 1.gamma., catalytic subunit, complexes with microcystin LR
RL: BIOL (Biological study)
(**crystn**. and **crystal** structure of, of human)

L117 ANSWER 54 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:156321 HCAPLUS
DN 120:156321
TI **Three-Dimensional** Solution Structure of Escherichia coli Periplasmic Cyclophilin
AU Clubb, Robert T.; Ferguson, Stephen B.; Walsh, Christopher T.; Wagner, Gerhard
CS Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, MA, 02115, USA
SO Biochemistry (**1994**), 33(10), 2761-72
CODEN: BICHAW; ISSN: 0006-2960
DT Journal
LA English
AB The soln. structure of the periplasmic cyclophilin type cis-trans peptidylprolyl isomerase from Escherichia coli (167 residues, MW > 18.200) has been detd. using multidimensional heteronuclear NMR spectroscopy and distance geometry calcns. The structure detn. is based on a total of 1720 NMR-derived restraints (1568 distance and 101 .phi. and 53 .chi.1 torsion angle restraints). Twelve distance geometry structures were calcd., and the av. root-mean-square (rms) deviation about the mean backbone coordinate positions is 0.84 .+-. 0.18 .ANG. for the backbone atoms of residues 5-165 of the ensemble. The **three-dimensional** structure of E. coli cyclophilin consists of an eight-stranded antiparallel .beta.-sheet barrel capped by .alpha.-helixes. The av. coordinates of the backbone atoms of the core residues of E. coli cyclophilin have an rms deviation of 1.44 .ANG., with conserved regions in the **crystal** structure of unligated human T cell cyclophilin [Ke, H. (1992) J. Mol. Biol. 228, 539-550]. Four regions proximal to the active site differ substantially and may det. protein substrate specificity, sensitivity to cyclosporin A, and the composite drug:protein surface required to inhibit **calcineurin**. A residue essential for isomerase activity in human T cell cyclophilin (His126) is replaced by Tyr122 in E. coli cyclophilin without affecting enzymic activity.

L117 ANSWER 55 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:134101 HCAPLUS
DN 120:134101
TI **Structure**-based design of an acyclic ligand that bridges **FKBP12** and **calcineurin**
AU Andrus, Merritt B.; Schreiber, Stuart L.
CS Dep. Chem., Harvard Univ., Cambridge, MA, 02138, USA
SO J. Am. Chem. Soc. (**1993**), 115(22), 10420-1
CODEN: JACSAT; ISSN: 0002-7863
DT Journal
LA English
GI



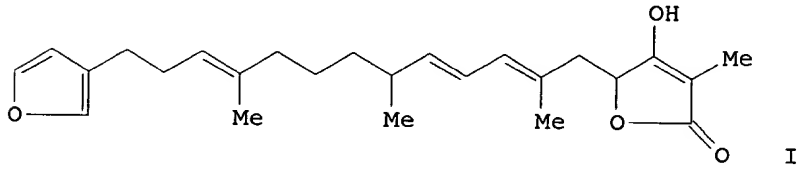
I

AB The high resoln. **x-ray crystal structure** of rapamycin (**FKBP12**)-**FK506** was used to design acyclic (seco) **FK506** variant I (termed SBL506 for seco bridging ligand related to **FK506**) that binds to **FKBP12** and forms an **FKBP12** complex that binds to **calcineurin**. The asym. total synthesis of SBL506 has been achieved in 37 steps. The synthesis of SBL506 and the detn. of its binding properties are reported.

IT **9025-75-6, Calcineurin**
RL: USES (Uses)
(inhibitors, acyclic truncated **FK 506** analogs)

IT **104987-11-3DP, FK 506**, acyclic truncated analogs
RL: PREP (Preparation)
(prepn. and **calcineurin** binding and inhibition of)

L117 ANSWER 56 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:102473 HCAPLUS
DN 120:102473
TI Isopalinurin: a mild protein phosphatase inhibitor from a southern Australian marine sponge, Dysidea sp
AU Murray, Leanne; Sim, Alistair T. R.; Rostas John A. P.; Capon, Robert J.
CS Sch. Chem., Univ. Melbourne, Parkville, 3052, Australia
SO Aust. J. Chem. (**1993**), 46(8), 1291-4
CODEN: AJCHAS; ISSN: 0004-9425
DT Journal
LA English
GI



I

AB A new sesterterpene tetronic acid, isopalinurin (I), has been isolated from an Australian marine sponge, Dysidea sp., collected in Bass Strait. I was identified as the agent responsible for the antibiotic activity and protein phosphatase inhibitory properties exhibited by the crude ethanol ext., and its structure was secured by detailed spectroscopic anal.

IT **9025-75-6**, Protein phosphatase
RL: PROC (Process)
(inhibition of, by sesterterpene of southern Australian marine sponge)

L117 ANSWER 57 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:100476 HCAPLUS
DN 120:100476
TI **Molecular model** of the A subunit of protein

phosphatase 2A; interaction with other subunits and tumor antigens
AU Ruediger, Ralf; Hentz, Marc; Fait, James; Mumby, Marc; Walter, Gernot
CS Dep. Pathol., Univ. California, San Diego, La Jolla, CA, 92093-0612, USA
SO J. Virol. (**1994**), 68(1), 123-9
CODEN: JOVIAM; ISSN: 0022-538X
DT Journal
LA English
AB Protein phosphatase 2A consists of three subunits, the catalytic subunit (C) and two regulatory subunits (A and B). The A subunit has a rod-like shape and consist of 15 nonidentical repeats. It binds the catalytic subunit through repeats 11 to 15 at the C terminus and the tumor antigens encoded by small DNA tumor viruses through overlapping but distinct regions at N-terminal repeats 2 to 8. A model of the A subunit was developed on the basis of the fact that uncharged or hydrophobic amino acids are conserved at eight defined positions within each repeat. Helical wheel projections suggested that each repeat can be arranged as two interacting amphipathic helixes connected by a short loop. Mutational anal. of the A subunit revealed that the proposed loops are important for binding of tumor antigens, the B subunit, and the C subunit. Native gel anal. of mutant A subunits synthesized in vitro demonstrated that the binding region for the B subunit, previously thought to include repeats 2 to 8, covers repeats 1 to 10 and that the B and C subunits cooperate in binding to the A subunit.
IT **9025-75-6**
RL: BIOL (Biological study)
(2A, A subunit of, structural model of and other subunits and tumor antigens interaction with)

L117 ANSWER 58 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:100213 HCAPLUS
DN 120:100213
TI Dephosphorylation of phosphopeptides by **calcineurin** (protein phosphatase 2B)
AU Donella-Deana, Arianna; Krinks, Marie H.; Ruzzene, Maria; Klee, Claude; Pinna, Lorenzo A.
CS Cent. Stud. Fisiol. Mitocondriale, Univ. Padova, Padua, Italy
SO Eur. J. Biochem. (**1994**), 219(1-2), 109-17
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB 38 (6-32 Residues) enzymically phosphorylated synthetic peptides have been assayed as substrates for **calcineurin**, a Ca2+/calmodulin-dependent protein phosphatase (PP-2B) belonging to the family of Ser/Thr-specific enzymes but also active on phosphotyrosine residues. Many peptides reproduce, with suitable modifications, naturally occurring phosphoacceptor sites. While protein phosphatases 2A and 2C are also very active on short phosphopeptides, an extended N-terminal stretch appears to be a necessary, albeit not sufficient, condition for an optimal dephosphorylation, comparable to that of protein substrates, of both phosphoseryl and phosphotyrosyl peptides by **calcineurin**. This finding corroborates the view that higher-order structure is an important determinant for the substrate specificity of **calcineurin**. However, a no. of shorter peptides are also appreciably dephosphorylated by this enzyme, their efficiency as substrates depending on local structural features. All the peptides that are appreciably dephosphorylated by **calcineurin** contain basic residue(s) on the N-terminal side. A basic residue located at position -3 relative to the phosphorylated residue plays a particularly relevant pos. role in detg. the dephosphorylation of short phosphopeptides. Acidic residue(s) adjacent to the C-terminal side of the phosphoamino acid are conversely powerful neg. determinants, preventing the dephosphorylation of otherwise suitable peptide substrates. However, **calcineurin** displays an only moderate preference of phosphothreonyl peptides which are conversely strikingly preferred over their phosphoseryl counterparts by the other classes of Ser/Thr-specific protein phosphatases. Moreover, **calcineurin** does not perceive as a strong neg. determinant the

motif Ser/Thr-Pro in peptides where this motif prevents dephosphorylation by the other classes of Ser/Thr protein phosphatases. Whenever tested on phosphotyrosyl peptides, **calcineurin** exhibits a specificity which is strikingly different from that of T-cell protein tyrosine phosphatase, a bona fide protein tyrosine phosphatase. In particular while the latter enzyme is esp. active toward a no. of phosphopeptides reproducing the phosphoacceptor sites of src products and of calmodulin whose N-terminal moieties are predominantly acidic, the artificial substrate phospho-angiotensin II, bearing an arginine residue at position -2, is far preferred by **calcineurin** over all phosphotyrosyl peptides of a similar size. Collectively taken these results show that the specificity of calcineruin, rather than resting on a given consensus sequence, is detd. by a variety of primary and higher-order structural features conferring to it an overall selectivity that is different from those of any other known protein phosphatase.

IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(2A and 2B and 2C and type 1, specificity for phosphopeptides of, substrate structure in relation to)

L117 ANSWER 59 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:69027 HCAPLUS
DN 120:69027
TI Cyclosporine- and **FK506**-induced sympathetic activation correlates with **calcineurin**-mediated inhibition of T-cell signaling
AU Lyson, Teresa; Ermel, LeAnn D.; Belshaw, Peter J.; Alberg, David G.; Schreiber, Stuart L.; Victor, Ronald G.
CS Southwest. Med. Cent., Univ. Texas, Dallas, TX, USA
SO Circ. Res. (**1993**), 73(3), 596-602
CODEN: CIRUAL; ISSN: 0009-7330
DT Journal
LA English
AB Cyclosporine A (CsA)-induced hypertension appears to be caused in part by neurogenic vasoconstriction, but the mechanism by which CsA activates the sympathetic nervous system is unknown. In T lymphocytes, the cellular target of CsA and the macrolide immunosuppressant **FK506** (as complexes with their endogenous cytoplasmic receptors, or immunophilins) is the Ca2+-calmodulin-dependent phosphatase **calcineurin**. The presence of **calcineurin** and its colocalization with immunophilin in the brain led the authors to hypothesize that the phosphatase also mediates CsA-induced sympathetic activation. The authors now report that sympathetic activity and arterial pressure in rats are increased not only by CsA but also **FK506**, which is structurally unrelated to CsA but inhibits the same **calcineurin**-sensitive T-cell signaling pathway. In contrast, sympathetic activity and blood pressure are not increased by rapamycin, which forms an immunophilin complex that does not bind **calcineurin**. Furthermore, CsA- and **FK506**-induced sympathetic activation is attenuated for drug analogs possessing modest changes in **mol. structure** in a way that closely parallels the ability of each analog to inhibit **calcineurin** -mediated T-cell signaling. These results implicate an important role for extralymphoid (ie., neuronal) **calcineurin** in mediating immunosuppressive drug toxicity.

IT **9025-75-6, Calcineurin**
RL: BIOL (Biological study)
(cyclosporin A and **FK506**-induced hypertension mediation by, of sympathetic nervous system)

IT **104987-11-3, FK506**
RL: BIOL (Biological study)
(sympathetic nervous system activation by, hypertension from, nerve **calcineurin** mediation of)

L117 ANSWER 60 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:3432 HCAPLUS
DN 120:3432

TI Bacterial and bacteriophage protein phosphatases
AU Koonin, Eugene V.
CS Natl. Cent. Biotechnol. Inf., Natl. Libr. Med., Bethesda, MD, 20894, USA
SO Mol. Microbiol. (**1993**), 8(4), 785-7
CODEN: MOMIEE; ISSN: 0950-382X
DT Journal
LA English
AB A comparison of the amino acid sequences of gene apaH-encoded diadenosine tetraphosphatase (I) from Escherichia coli and Klebsiella aerogenes with those of **phosphoprotein phosphatase** (II) from phages .lambda. and phi80 and the eukaryotes, Drosophila melanogaster, Saccharomyces cerevisiae, and rabbit, showed significant homol. between gene apaH-encoded I and phage II. The probability that the similarity between these 2 proteins was due to chance alone was **computed** to be .apprx.2 .times. 10-5. Remarkably, phage II was much more closely related to I than it was to II from the eukaryotes. Thus, phosphatases attacking very different types of substrates may share a common ancestry, and perhaps also functional similarities. An interesting question for future research is whether or not a bacterial gene exists coding for a II related to I and phage II.
IT **9025-75-6, Phosphoprotein phosphatase**
RL: PRP (Properties); BIOL (Biological study)
(amino acid sequence of, of phages, bacterial gene apaH-encoded diadenosine tetraphosphatase sequence homol. with, evolution in relation to)

L117 ANSWER 61 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1994:2549 HCAPLUS
DN 120:2549
TI The conserved acid binding domain **model** of inhibitors of protein phosphatases 1 and 2 A: **molecular modeling** aspects
AU Quinn, Ronald J.; Taylor, Cherie; Suganuma, Masami; Fujiki, Hirota
CS Sch. Sci., Griffith Univ., Brisbane, 4111, Australia
SO Bioorg. Med. Chem. Lett. (**1993**), 3(6), 1029-34
CODEN: BMCLE8; ISSN: 0960-894X
DT Journal
LA English
AB Using **mol. modeling**, three chem. distinct members of the okadaic acid class or protein phosphatase inhibitors and tumor promoters, okadaic acid, calyculin A and microcystin-LR were fitted together. The **mol. modeling** results indicate a pharmacophore **model** consisting of a central core, contg. one conserved acidic group and two potential hydrogen bonding sites, and a non-polar side chain.
IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(1 and 2A, inhibitors, **mol. modeling** of, as tumor promoters, pharmacophore identification in)

L117 ANSWER 62 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:622464 HCAPLUS
DN 119:222464
TI Functionally distinct phospho-forms underlie incremental activation of protein kinase-regulated chloride conductance in mammalian heart
AU Hwang, Tzyh Chang; Horie, Minoru; Gadsby, David C.
CS Lab. Card./Membr. Physiol., Rockefeller Univ., New York, NY, 10021, USA
SO J. Gen. Physiol. (**1993**), 101(5), 629-50
CODEN: JGPLAD; ISSN: 0022-1295
DT Journal
LA English
AB The regulation of cardiac Cl- conductance by cAMP-dependent protein kinase (PKA) and cellular phosphatases was studied in isolated guinea pig ventricular myocytes by using wide-tipped, perfusion pipets to record whole-cell currents. Exposure to forskolin (Fsk) or isoproterenol (Iso) elicits a Cl- conductance that results exclusively from PKA-dependent phosphorylation because it can be completely abolished, or its activation

fully prevented, by switching to pipet soln. contg. PKI, a synthetic peptide inhibitor of PKA. The Cl- conductance activated by micromolar concns. of either agonist reached its steady-state amplitude in 1-2 min and was deactivated promptly and entirely, usually within 2 min, upon washing out the agonist, implying a continuous high level of activity of endogenous protein phosphatases. Accordingly, intracellular application of okadaic acid or microcystin, both potent inhibitors of protein phosphatases 1 and 2A, during exposure to Fsk enhanced the steady-state Cl- conductance and slowed its deactivation after washing out the Fsk. Maximal potentiation of the conductance, by .apprx.60%, was obtained with pipet concns. of .apprx.10 .mu.M okadaic acid (or .apprx.5 .mu.M **microcrystin**) and did not result from an increase in the apparent affinity for Fsk. In the presence of maximally effective concns. of okadaic acid and/or microcystin, deactivation of the enhanced Cl- conductance upon washout of agonist was incomplete, with about half of the conductance persisting indefinitely. That residual conductance did not reflect continued action of PKA because it was insensitive to PKI, but was identified as a fraction of the activated Cl- conductance by its biophys. characteristics. The results suggests that complete deactivation of the PKA-regulated cardiac Cl- conductance requires dephosphorylation by a type 1 and/or 2A phosphatase, but that partial deactivation can be accomplished by activity of some other phosphatase(s). These findings are consistent with sequential phosphorylation of a protein, probably the Cl- channel itself, at two different kinds of sites. The resulting phosphoproteins can be distinguished on the basis of their different contributions to whole-cell Cl- conductance.

IT **9025-75-6**
RL: BIOL (Biological study)
(chloride conductance by heart ventricle myocytes regulation by, phosphorylated forms of channel proteins in relation to)

L117 ANSWER 63 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:576300 HCAPLUS
DN 119:176300
TI Inhibitors of protein phosphatases
AU Suganuma, Masami; Fujiki, Hirota
CS Cancer Prev. Div., Natl. Cancer Cent. Res. Inst., Tokyo, 104, Japan
SO Tanpakushitsu Kakusan Koso (**1993**), 38(11), 1960-70
CODEN: TAKKAJ; ISSN: 0039-9450
DT Journal; General Review
LA Japanese
AB A review with 31 refs., on the structure-activity relations of **phosphoprotein phosphatase** inhibitors, okadaic acid, calyculin A, microcystin, their derivs., and tautomycin. Their inhibitory interactions with **phosphoprotein phosphatases** of different types are discussed.
IT **9025-75-6**, Protein phosphatase
RL: PROC (Process)
(inhibition of, by okadaic acid-related compds.)

L117 ANSWER 64 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:554618 HCAPLUS
DN 119:154618
TI Expression, purification, **crystallization**, and biochemical characterization of a recombinant protein phosphatase
AU Zhuo, Shaoqiu; Clemens, James C.; Hakes, David J.; Barford, David; Dixon, Jack E.
CS Med. Sch., Univ. Michigan, Ann Arbor, MI, 48109-0606, USA
SO J. Biol. Chem. (**1993**), 268(24), 17754-61
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB A protein phosphatase (PPase) from the bacteriophage .lambda. was overexpressed in Escherichia coli. The recombinant enzyme was purified to homogeneity yielding approx. 17 mg of enzyme from a single liter of bacterial culture. Biochem. characterization of the enzyme showed that it

required Mn2+ or Ni2+ as an activator. The recombinant enzyme was active toward serine, threonine, and tyrosine phosphoproteins and phosphopeptides. Surprisingly, the bacterial histidyl phosphoprotein, NRII, was also dephosphorylated by the .lambda.-PPase. The .lambda.-PPase shares a no. of kinetic and structural properties with the eukaryotic Ser/Thr phosphatases, suggesting that the .lambda.-PPase will serve as a good model for **structure**-function studies. **Crystn.** of the recombinant purified .lambda.-PPase yielded monoclinic **crystals**. The **crystals** diffract to 4.0 .ANG. when exposed to synchrotron **x-ray** radiation.

IT **9025-75-6P, Phosphoprotein phosphatase**
RL: PREP (Preparation)
(of bacteriophage .lambda., purifn. and **crystal structure** and substrate specificity of)

L117 ANSWER 65 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:551494 HCAPLUS
DN 119:151494
TI **FK-506** - a novel immunosuppressant
AU Parsons, William H.; Sigal, Nolan H.; Syvratt, Matthew J.
CS Dep. Basic Med. Chem., Merck Res. Lab., Rahway, NJ, 07065, USA
SO Ann. N. Y. Acad. Sci. (**1993**), 685(Immunomodulating Drugs), 22-36
CODEN: ANYAA9; ISSN: 0077-8923
DT Journal; General Review
LA English
AB A review, with 50 refs., of **FK-506**; structure, **conformation**, clin. and exptl. immunosuppressant activity and interactions with **calcineurin** are discussed.
IT **104987-11-3, FK-506**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant activity of)

L117 ANSWER 66 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:489984 HCAPLUS
DN 119:89984
TI Tertiary **structure** of **calcineurin** B by homology modeling
AU West, Susan; Bamborough, Paul; Tully, Roger
CS Dyson Perrins Lab., Univ. Oxford, Oxford, UK
SO J. Mol. Graphics (**1993**), 11(1), 47-52, 45
CODEN: JMGRDV; ISSN: 0263-7855
DT Journal
LA English
AB The **crystal structure** of the calcium-binding protein calmodulin is used to model the immunol. important **calcineurin** subunit B. The rough **structure** is produced by **computer** -aided homol. modeling. Refinement of this using mol. dynamics leads to a suggested **structure** which appears to satisfy reasonable hydrophilicity and hydrogen-bonding criteria. In the absence of a **crystal structure**, the model may prove useful in modeling of its interactions with the phosphatase catalytic subunit **calcineurin** A, and help to explain the calcium modulation of this protein.
IT **9025-75-6, Calcineurin**
RL: BIOL (Biological study)
(subunit B, tertiary **structure** of, homol. modeling of)

L117 ANSWER 67 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:485446 HCAPLUS
DN 119:85446
TI Comparison of **conformations** of cyclosporin A and macrolide **FK506** fragments: localization of putative binding sites with phosphatase **calcineurin**
AU Denesyuk, Alexander I.; Korpela, Timo; Lundell, Juhani; Sara, Rolf; Zav'yalov, Vladimir P.

CS Inst. Immunol., Lyubuchany, 142380, Russia
SO Biochem. Biophys. Res. Commun. (**1993**), 194(1), 280-6
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB The **three-dimensional structures** of two immunosuppressants, cyclosporin A and macrolide **FK506**, were compared. The sites N-methylglycine3-N-methylleucine4 and valine5-N-methylleucine6 of cyclosporin A were found to be similar to each other (the root-mean-square value was 0.29 .ANG. for six ref. points of the main chain) and also to the site C17-C22 of **FK506** (the root-mean-square values were 0.33 .ANG. and 0.13 .ANG., resp.). The authors suggest that these fragments of cyclosporin A and **FK506** make a major contribution to the interaction of the immunosuppressants with the phosphatase **calcineurin**.
IT **104987-11-3, FK506**
RL: PRP (Properties)
(**conformation** of, binding to phosphatase **calcineurin** in relation to)
IT **9025-75-6, Calcineurin**
RL: BIOL (Biological study)
(cyclosporin A and **FK506** binding to, **conformation structure** in relation to)

L117 ANSWER 68 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:440508 HCAPLUS
DN 119:40508
TI **FK-506**-binding protein: **Three-dimensional** structure of the complex with the antagonist L-685,818
AU Becker, Joseph W.; Rotonda, Jennifer; McKeever, Brian M.; Chan, H. Karen; Marcy, Alice I.; Wiederrecht, Greg; Hermes, Jeffrey D.; Springer, James P.
CS Dep. Biophys. Chem., Merck Res. Lab., Rahway, NJ, 07065-0900, USA
SO J. Biol. Chem. (**1993**), 268(15), 11335-9
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB L-685818 differs only slightly in structure from the immunosuppressive drug **FK-506** and both compds. bind with a comparable affinity to the 12-kDa **FK-506**-binding protein (FKBP12), the major intracellular receptor for the drug. Despite these similarities, L-685818 is a potent antagonist of the immunosuppressive and toxic effects of **FK-506**. Although **FK-506** and L-685818 differ greatly in pharmacol., the 3-dimensional structures of their complexes with FKBP12 are essentially identical. Approx. half of each ligand is in contact with the receptor protein and half is exposed to solvent; the exposed region includes the 2 sites where the compds. differ. Thus, the profound differences in the pharmacol. of these 2 compds. are not caused by differences in their interactions with FKBP12. The differences may arise because relatively minor changes in the exposed part of the bound ligand may have strong effects on how FKBP12-ligand complexes interact with **calcineurin**, their putative intracellular target. **FK-506** complexes with FKBP12 proteins from several species inhibit mammalian **calcineurin**. Anal. of the 3-dimensional structure of the complexes with respect to residues conserved among these proteins suggests a small no. of surface residues near the bound ligands that may play a crit. role in interactions between the protein-drug complex and **calcineurin**.
IT **104987-11-3, FK-506**
RL: BIOL (Biological study)
(binding protein complexes with L-685818 and, structure of, pharmacol. implications of)

L117 ANSWER 69 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:440256 HCAPLUS
DN 119:40256
TI Immunosuppressive activity of [MeBm2t]1-, D-diaminobutyryl-8-, and

D-diaminopropyl-8-cyclosporin analogs correlates with inhibition of **calcineurin** phosphatase activity

AU Nelson, Patricia A.; Akselband, Yeugenya; Kawamura, Akinori; Su, Michael; Tung, Roger D.; Rich, Daniel H.; Kishore, Vimal; Rosborough, Sandra L.; DeCenzo, Maureen T.; et al.

CS Vertex Pharma. Inc., Cambridge, MA, 02139, USA

SO J. Immunol. (**1993**), 150(6), 2139-47
CODEN: JOIMA3; ISSN: 0022-1767

DT Journal

LA English

AB **Calcineurin**, a Ca2+/calmodulin-dependent protein phosphatase, has recently been identified as a common target for cyclophilin A-cyclosporin A and **FK506** binding protein 12-**FK506** complexes. This study has examd. the structure activity relationships of cyclosporin A (CsA) and three functionally distinct analogs, [MeBm2t]1-CsA, D-diaminobutyryl-8-CsA (Dab8-CsA), and D-diaminopropyl-8-CsA (Dap8-CsA). Immunosuppressive potency in T cell activation models, NF.kappa.B activation, and IL-2 mRNA transcription has been compared with analog affinity for cyclophilin A and inhibition of **calcineurin** phosphatase activity. CsA, Dap8-CsA, and Dab8-CsA bind to cyclophilin A with a similar affinity (Ki 4 to 5 nM as measured by inhibition of prolyl cis-trans isomerase activity), however, Dap8-CsA and Dab8-CsA inhibit T cell activation less than CsA. Although [MeBm2t]-CsA has weak affinity for cyclophilin A (Ki 540 nM), its immunosuppressive potency is similar to that of CsA. Both cyclophilin A-CsA and cyclophilin A-[MeBm2t]1-CsA complexes inhibit **calcineurin** phosphatase activity in vitro (Ki 114 and 67 nM, resp.). In Jurkat cells exposed to CsA or the analogs for 2 h, endogenous **calcineurin** phosphatase activity in cell lysates was inhibited by CsA and [MeBm2t]1 (drug concns. causing 50% redn. in 32PO4 release of 8 and 55 nM, resp.) in proportion to inhibition of T cell activation, IL-2 mRNA transcription, and NF.kappa.B activation. Dap8-CsA and Dab8-CsA had a minimal effect on endogenous **calcineurin** phosphatase activity in Jurkat cell lysates. These findings correlate the functional activity of CsA and structural analogs with **calcineurin** phosphatase activity and support **calcineurin** as a target for drug action. The Dap8 and Dab8 modifications of CaA, occurring in residue 8, which is exposed to solvent in the cyclophilin A-CsA complex, appears to significantly alter complex affinity for **calcineurin**.

IT **9025-75-6**, **Calcineurin** phosphatase
RL: BIOL (Biological study)
(inhibition of, by cycloslporin A analog-cyclophilin A complexes, immunosuppression in relation to)

L117 ANSWER 70 OF 126 HCAPLUS COPYRIGHT 2000 ACS

AN 1993:440242 HCAPLUS

DN 119:40242

TI Structure-activity profiles of macrolactam immunosuppressant **FK-506** analogs

AU Kawai, Megumi; Lane, Benjamin C.; Hsieh, Gin C.; Mollison, Karl W.; Carter, George W.; Luly, Jay R.

CS Pharm. Prod. Div., Abbott Lab., Abbott Park, IL, 60064, USA

SO FEBS Lett. (**1993**), 316(2), 107-13
CODEN: FEBLAL; ISSN: 0014-5793

DT Journal

LA English

AB The immunosuppressive agent **FK-506** has received much attention due to its efficacy and potency in the areas of transplant rejection and autoimmune disease. **Calcineurin**, a Ca2+-calmodulin activated phosphatase, was recently implicated in the immunosuppressive mechanism of **FK-506**. In their ongoing search for superior immunosuppressive agents, the authors have synthesized several analogs of **FK-506** and tested their mechanistic and immunosuppressive actions. It was found that C-18 hydroxyl analogs of ascomycin, an analog of **FK-506** also called FR900520, bound tightly to immunophilin FKBP-12, but do not show any immunosuppressive activity in vitro or in vivo despite good

bioavailability. Further, they reverse the inhibition of **calcineurin** caused by **FK-506**/FKBP-12 complex.

IT **104987-11-3, FK506**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant activity of, mechanism and structure in relation to, in humans and lab. animals)

IT **9025-75-6, Calcineurin** phosphatase
RL: PROC (Process)
(inhibition of, by **FK-506**-FKBP-12 complex, hydroxyascomycin analogs reversal of)

L117 ANSWER 71 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:406826 HCAPLUS
DN 119:6826
TI Novel monoclonal antibodies that differentiate between the binding of pp60c-src or protein phosphatase 2A by polyomavirus middle T antigen
AU Dilworth, Stephen M.; Horner, Victoria P.
CS Dep. Chem. Pathol., R. Postgrad. Med. Sch., London, W12 0NN, UK
SO J. Virol. (**1993**), 67(4), 2235-44
CODEN: JOVIAM; ISSN: 0022-538X
DT Journal
LA English
AB Fourteen pGEX plasmids that express defined regions of polyomavirus middle T antigen in bacteria have been constructed. These polypeptides were used to generate 18 new monoclonal antibodies directed against the unique portion of middle T and to map the approx. position of the antibody recognition sites onto the protein sequence. All of the antibodies effectively immunoppt. middle T and the assocd. 60 and 35 kD components of protein phosphatase 2A. Four of the antibodies, however, do not react with middle T when it is bound to pp60c-src. These four probably bind to amino acids 203-218 of the middle T protein sequence, which are encoded by the mRNA immediately 3' to the splice junction that creates the C-terminal unique region. This suggests that addnl. middle T sequences are required for middle T's interaction with pp60c-src than are needed for its binding to protein phosphatase 2A. The antibodies localize this extra region and provide a means of distinguishing between these two assocns.

IT **9025-75-6**
RL: PRP (Properties)
(polyoma virus middle T antigen assocn. with, monoclonal antibody study of)

L117 ANSWER 72 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:265152 HCAPLUS
DN 118:265152
TI Correlation of backbone amide and aliphatic side-chain resonances in 13C/15N-enriched proteins by isotropic mixing of carbon-13 magnetization
AU Grzesiek, Stephan; Anglister, Jacob; Bax, Ad
CS Lab. Chem. Phys., Natl. Inst. Diabetes Dig. Kidney Dis., Bethesda, MD, 20892, USA
SO J. Magn. Reson., Ser. B (**1993**), 101(1), 114-19
CODEN: JMRBE5; ISSN: 1064-1866
DT Journal
LA English
AB Two 3-dimensional (**3D**) NMR expts., designated H(CCO)NH and C(CO)NH, are described that can correlate all the 1H or 13C resonances of a given amino acid directly with the amide of the next residue. The new methods are far more convenient for obtaining assignments than the previous combinations of H2O and D2O expts., as they provide a direct linkage between the backbone and entire side chains. Pulse schemes for the C(CO)NH and H(CCO)NH expts. are shown and strip plots are presented of the illustrative correlations obsd. for the amides of residues Gly-121 to Leu-129 of **calcineurin** B taken from spectra obtained by using the new methods.

L117 ANSWER 73 OF 126 HCAPLUS COPYRIGHT 2000 ACS

AN 1993:246943 HCAPLUS
DN 118:246943
TI Improved **calcineurin** inhibition by yeast **FKBP12**-drug complexes. **Crystallographic** and functional analysis
AU Rotonda, Jennifer; Burbaum, Jonathan J.; Chan, H. Karen; Marcy, Alice I.; Becker, Joseph W.
CS Dep. Biophys. Chem., Merck Res. Lab., Rahway, NJ, 07065-0900, USA
SO J. Biol. Chem. (**1993**), 268(11), 7607-9
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The protein phosphatase **calcineurin** is the putative target for the immunosuppressive drug **FK-506**. The enzyme is inhibited by the complex of the drug with its intracellular receptor, the 12-kDa **FK-506**-binding protein (**FKBP12**), and the strength of inhibition usually correlates strongly with immunosuppressive potency. We find, however, that the complex of yeast **FKBP12** with L-685,818, a well characterized antagonist of **FK-506** immunosuppression, is a potent inhibitor of **calcineurin**. The corresponding human complex does not inhibit the enzyme, and both human and yeast complexes with **FK-506** do inhibit. To understand the structural basis of these findings, we have detd. the **three-dimensional structure** of the complex of yeast **FKBP12** with **FK-506** by **x-ray crystallog.**, and have found that the **structure** of the yeast complex is strikingly similar to its human homolog. These observations indicate that specific sequence elements in the yeast protein provide stronger binding interactions with a heterologous **calcineurin** than do the corresponding elements in the human protein, and suggest structural modifications that may improve the potency of this class of immunosuppressants.
IT **104987-11-3, FK-506**
RL: BAC (Biological activity or effector, except adverse); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(immunosuppressant activity of, **FKBP-12** complex inhibition of **calcineurin** in, **structure** in relation to)
IT **9025-75-6, Calcineurin**
RL: PROC (Process)
(inhibition of, by **FK-506** complex with **FKBP -12**, **structure** in, immunosuppressant activity in relation to)

L117 ANSWER 74 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:226864 HCAPLUS
DN 118:226864
TI Automated DNA sequencing and analysis of 106 kilobases from human chromosome 19q13.3
AU Martin-Gallardo, A.; McCombie, W. R.; Gocayne, J. D.; FitzGerald, M. G.; Wallace, S.; Lee, B. M. B.; Lamerdin, J.; Trapp, S.; Kelley, J. M.; et al.
CS Recept. Biochem. Mol. Biol. Sect., Natl. Inst. Neurol. Disord. Stroke, Bethesda, MD, 20892, USA
SO Nat. Genet. (**1992**), 1(1), 34-9
CODEN: NGENEC; ISSN: 1061-4036
DT Journal
LA English
AB A total of 116,118 base pairs (pb) derived from 3 cosmids spanning the ERCC1 locus of human chromosome 19q13.3 were sequenced with automated fluorescence-based sequencers and analyzed by PCR amplification and **computer** methods. The assembled sequence forms 2 contigs totalling 105,831 bp, which contain a human fosB proto-oncogene, a gene encoding a protein phosphatase, 2 genes of unknown function, and the previously characterized ERCC1 DNA repair gene. This light band region has a high av. d. of 1.4 Alu repeats/kilobase. Human chromosome light bands could therefore contain up to 75,000 genes and 1.5 million Alu repeats.

IT **9025-75-6**, Protein phosphatase
RL: PRP (Properties)
(amino acid sequence of, encoded by chromosome 19q13.3 of human)

L117 ANSWER 75 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:164109 HCAPLUS
DN 118:164109
TI Active site mutants of human cyclophilin A separate peptidyl-prolyl isomerase activity from cyclosporin A binding and **calcineurin** inhibition
AU Zydowsky, Lynne D.; Etzkorn, Felicia A.; Chang, Howard Y.; Ferguson, Stephen B.; Stolz, Lesley A.; Ho, Susanna I.; Walsh, Christopher T.
CS Dep. Biol. Chem. Mol. Pharmacol., Harvard Med. Sch., Boston, MA, 02115, USA
SO Protein Sci. (**1992**), 1(9), 1092-9
CODEN: PRCIEI
DT Journal
LA English
AB Based on recent **x-ray** structural information, 6 site-directed mutants of human cyclophilin A (hCyPA) involving residues in the putative active site (His-54, Arg-55, Phe-60, Gln-111, Phe-113, and His-126) were constructed, overexpressed, and purified from Escherichia coli to homogeneity. Mutant proteins W121A, H54Q, R55A, F60A, Q111A, F113A, and H126Q were assayed for peptidylprolyl cis-trans-isomerase (PPIase) activity, their ability to bind the immunosuppressive drug, cyclosporin A (CsA), and **phosphoprotein phosphatase** 2B (**calcineurin**) inhibition in the presence of CsA. The results indicated that H54Q, Q111A, F113A, and W121A retained 3-15% of the catalytic efficiency (kcat/Km) of wild-type recombinant hCyPA. The remaining 3 mutants (R55A, F60A, and H126Q) each retained <1% of the wild-type catalytic efficiency, indicating the participation of these residues in PPIase catalysis. Each of the mutants bound to a CsA affinity matrix. Mutants R55A, F60A, F113A, and H126Q inhibited **calcineurin** in the presence of CsA, whereas W121A did not. Although CsA is a competitive inhibitor of PPIase activity, was able to complex with enzymically inactive cyclophilins and inhibit the phosphatase activity of **calcineurin**.
IT **9025-75-6**
RL: BIOL (Biological study)
(inhibition of **calcineurin**, by human cyclophilin A peptidylprolyl isomerase in cyclosporin A presence, active site mutations effect on)

L117 ANSWER 76 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:139435 HCAPLUS
DN 118:139435
TI **X-ray** structure of a decameric cyclophilin-cyclosporin **crystal** complex
AU Pfluegl, Gaston; Kallen, Joerg; Schirmer, Tilman; Jansonius, Johan N.; Zurini, Mauro G. M.; Walkinshaw, Malcolm D.
CS Preclin. Res., Sandoz Pharma AG, Basel, 4002, Switz.
SO Nature (London) (**1993**), 361(6407), 91-4
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB Human cyclophilin A (CypA), a ubiquitous intracellular protein of 165 amino acids, is the major receptor for the cyclic undecapeptide immunosuppressant drug cyclosprin A (CsA), which prevents allograft rejection after transplant surgery and is efficacious in the field of autoimmune diseases, CsA prevents T-cell proliferation by blocking the calcium-activated pathway leading to interleukin-2 transcription. Besides their ability to bind CsA, the cyclophilin isoforms also have peptidyl-prolyl isomerase activity and enhance the rate of protein folding. The macrolide **FK506** acts similarly to CsA and its cognate receptor FKBP also has peptidyl-prolyl isomerase activity. Inhibition of this enzymic activity alone is not sufficient to achieve

immunosuppression. A direct mol. interaction between the drug-immunophilin complex (CsA-CypA, or **FK506**-FKBP) and the phosphatase **calcineurin**, is responsible for modulating the T-cell receptor signal transduction pathway. Here the authors describe the **crystal** structure of a decameric CypA-CsA complex. The **crystallog**. asym. unit is composed of a pentamer of 1:1 cyclophilin-cyclosporin complexes of rather exact non-**crystallog** . fivefold symmetry. The 2.8 .ANG. electron d. map is of high quality. The five independent cyclosporin mols. are clearly identifiable, providing an unambiguous picture of the detailed interactions between a peptide drug and its receptor. It broadly confirms the results of previous NMR, **X-ray** and modeling studies, but provides further important structural details which will be of use in the design of drugs that are analogs of CsA.

L117 ANSWER 77 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:139434 HCAPLUS
DN 118:139434
TI Solution structure of the cyclosporin A/cyclophilin complex by NMR
AU Theriault, Yves; Logan, Timothy M.; Meadows, Robert; Yu, Liping; Olejniczak, Edward T.; Holzman, Thomas F.; Simmer, Robert L.; Fesik, Stephen W.
CS Pharm. Discovery Div., Abbott Lab., Abbott Park, IL, 60064, USA
SO Nature (London) (**1993**), 361(6407), 88-91
CODEN: NATUAS; ISSN: 0028-0836
DT Journal
LA English
AB Cyclosporin A, a cyclic undecapeptide, is a potent immunosuppressant that binds to a peptidyl-prolyl cis-trans isomerase of 165 amino acids, cyclophilin. The cyclosporin A/cyclophilin complex inhibits this calcium- and calmodulin-dependent phosphatase, **calcineurin**, resulting in a failure to activate genes encoding interleukin-2 and other lymphokines. The **three-dimensional** structures of uncomplexed cyclophilin, a tetrapeptide/cyclophilin complex, and cyclosporin A when bound to cyclophilin have been reported. However, the structure of the cyclosporin A/cyclophilin complex has not been detd. Here the authors soln. structure of the cyclosporin A/cyclophilin complex obtained by heteronuclear **three-dimensional** NMR spectroscopy. The structure, one of the largest detd. by NMR, differs from proposed models of the complex and is analyzed in terms of the binding interactions and structure/activity relationships for CsA analogs.

L117 ANSWER 78 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:120353 HCAPLUS
DN 118:120353
TI Identification of tissue proteins by amino acid analysis after purification by two-dimensional electrophoresis
AU Jungblut, P.; Dzionara, M.; Klose, J.; Wittmann-Leibold, B.
CS Inst. Toxikol. Embryonalpharmakol., Freie Univ. Berlin, Berlin, 1000/33, Germany
SO J. Protein Chem. (**1992**), 11(6), 603-12
CODEN: JPCHD2; ISSN: 0277-8033
DT Journal
LA English
AB Mouse brain proteins were sepd. by two-dimensional electrophoresis (2-DE). The proteins of a section of the 2-DE pattern were blotted onto hydrophobic membranes and 43 of them were excised and hydrolyzed by liq.-phase hydrolysis. The amino acid compn. of these proteins was detd. by orthophthaldialdehyde precolumn derivatization and compared with the compns. of known proteins stored in the NBRF sequence **database**. An identification program named ASA was developed for this purpose. The ASA program includes correction and weighting factors, data redn. by mol. wt. windows, and exclusion or inclusion of certain organisms as desired. As a control, eight test proteins and five well-known proteins from mouse brain, all sepd. by 2-DE, were correctly identified by the program. Out of the 43 brain proteins selected, 19 were identified with high

confidence.
IT **9025-75-6**
RL: ANT (Analyte); ANST (Analytical study)
(detection of, in tissue by 2-dimensional electrophoresis and amino acid anal.)

L117 ANSWER 79 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:96638 HCAPLUS
DN 118:96638
TI Model for the role of macromolecular crowding in regulation of cellular volume. [Erratum to document cited in CA118(5):34753t]
AU Minton, Allen P.; Colclasure, G. Craig; Parker, John C.
CS Lab. Biochem. Pharmacol., Natl. Inst. Diabetes, Dig. Kidney Dis., Bethesda, MD, 20892, USA
SO Proc. Natl. Acad. Sci. U. S. A. (**1993**), 90(3), 1137
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB An error in the figure for a reaction scheme has been cor. The error was not reflected in the abstr. or the index entries.
IT **9025-75-6**
RL: BIOL (Biological study)
(in cell vol. regulation model (Erratum))

L117 ANSWER 80 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:34753 HCAPLUS
DN 118:34753
TI Model for the role of macromolecular crowding in regulation of cellular volume
AU Minton, Allen P.; Colclasure, G. Craig; Parker, John C.
CS Lab. Biochem. Pharmacol., Natl. Inst. Diabetes, Dig. Kidney Dis., Bethesda, MD, 20892, USA
SO Proc. Natl. Acad. Sci. U. S. A. (**1992**), 89(21), 10504-6
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB A simple model is proposed to account for large increases in transporter-mediated ion flux across cell membranes that are elicited by small fractional changes of cell vol. The model is based upon the concept that, as a result of large excluded vol. effects in cytoplasm (macromol. crowding), the tendency of sol. macromols. to assoc. with membrane proteins is much more sensitive to changes in cell water content than expected on the basis of simple considerations of mass action. The model postulates that an ion transporter may exist in either an active dephosphorylated state or an inactive phosphorylated state and that the steady-state activity of the transporter reflects a balance between the rates of phosphatase-catalyzed activation and kinase-catalyzed inactivation. Cell swelling results in the inhibition of kinase relative to phosphatase activity, thereby increasing the steady-state concn. of the active form of the transporter. Calcd. vol.-dependent stimulation of ion flux is comparable to that obsd. exptl.
IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(in cell vol. regulation model)

L117 ANSWER 81 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1993:17219 HCAPLUS
DN 118:17219
TI Isolation and sequence determination of the plant homolog of the eukaryotic initiation factor 4D cDNA from alfalfa, Medicago sativa
AU Pay, Aniko; Heberle-Bors, Erwin; Hirt, Heribert
CS Inst. Microbiol. Gent., Univ. Vienna, Vienna, A-1090, Austria
SO Plant Mol. Biol. (**1991**), 17(4), 927-9
CODEN: PMBIDB; ISSN: 0167-4412
DT Journal
LA English

AB Eukaryotic translation initiation factor 4D (eIF4D) is a protein of 16-18 kDa. The precise function of eIF4D in protein synthesis is not known. It appears to be involved either in ribosomal subunit joining or in the formation of the 80S initiation complex. Here, the isolation of the first eIF4D cDNA clone from the plant kingdom is reported. The eIF4D cDNA clone was fortuitously isolated from an alfalfa cDNA library prepd. from suspension culture cells that had been challenged for 48 h with 100 .mu.M 2,4-dichlorophenoxy-acetic acid to induce somatic embryogenesis. The probe used for screening was a PCR fragment with homol. to **phosphoprotein phosphatases**. The length of the eIF4D clone is 742 nucleotides. A **computer**-assisted search for amino acid homologies revealed significant similarity to eIF4D proteins from human, rabbit, yeast, and Dictyostelium. Interestingly, the yeast eIF4D showed a considerably higher identity score, i.e. of 58.7% than both the human and rabbit proteins (both 50.6% identity). Among all proteins, the most conserved region consists of a sequence of 12 amino acids at position 46 to 57. This region embeds the post-translational modification site of the lysine residue to hypusine (position 51) that is crucial to eIF4D activity. Another interesting feature is that the plant and yeast amino termini are highly similar to each other but are highly different from their mammalian counterparts. This difference may have functional significance.

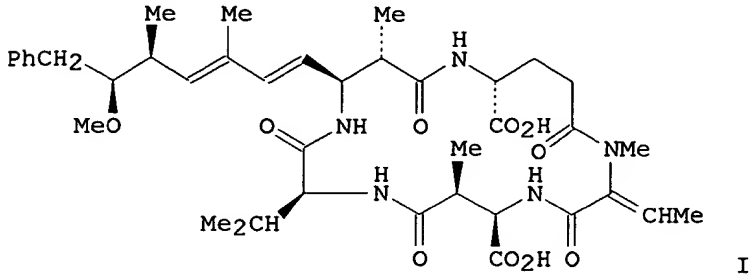
L117 ANSWER 82 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:565653 HCAPLUS
DN 117:165653
TI Inhibitory effect of okadaic acid derivatives on protein phosphatases. A study on **structure**-affinity relationship
AU Takai, Akira; Murata, Michio; Torigoe, Koichiro; Isobe, Minoru; Mieskes, Gottfried; Yasumoto, Takeshi
CS Sch. Med., Nagoya Univ., Nagoya, 466, Japan
SO Biochem. J. (**1992**), 284(2), 539-44
CODEN: BIJOAK; ISSN: 0306-3275
DT Journal
LA English
AB The effect of structural modifications of okadaic acid (OA), a polyether C38 fatty acid, was studied on its inhibitory activity toward type 1 and type 2A protein phosphatase (PP1 and PP2A) by using OA derivs. obtained either by isolation from natural sources or by chem. processes. The dissocn. const. (Ki) for the interaction of OA with PP2A was estd. to be 30 (26-33) nM [median (95% confidence limits)]. The OA derivs. used and their affinity for PP2A, expressed as Ki (in brackets) were as follows: 35-methyl-OA (DTX1)[19 (12-25)pM], OA-9,10-episulfide (acanthifolicin) [47 (25-60) pM], 7-deoxy-OA [69 (31-138] pM], 14,15-dihydro-OA [315 (275-360) pM], 2-deoxy-OA [899 (763-1044) pM], 7-O-palmitoyl-OA [>100 nM], 7-O-palmitoyl-DTX1 [>100 nM], Me okadaate [.mchgt.100 nM], 2-oxo-decarboxy-OA [.mchgt.100 nM] and the C-15-C-38 fragment of OA [.mchgt.100 nM]. The sequence of the affinity of these derivs. for PP1 was essentially the same as that obsd. with PP2A, although the abs. values of Ki were very different for the enzymes. The inhibitory effect of OA on PP2A was reversed by applying a murine monoclonal antibody against OA, which recognizes modifications of the 7-hydroxyl group of the OA mol. It has been shown by NMR spectroscopy and **x-ray** anal. that one end (C-1-C-24) of the OA mol. assumes a circular **conformation**. The present results suggest the importance of the **conformation** for the inhibitory action of OA on the protein phosphatases. The ratios of the Ki values for PP1 to that for PP2A, which were within the range 103-104, tended to be smaller for the derivs. with lower affinity, indicating that the structural changes in OA impaired the affinity for PP2A more strongly than that for PP1.
IT **9025-75-6**
RL: BIOL (Biological study)
(type 1 and 2, okadaic acid derivs. effect on, **mol. structure** in relation to)

L117 ANSWER 83 OF 126 HCAPLUS COPYRIGHT 2000 ACS

AN 1992:563513 HCAPLUS
DN 117:163513
TI **Conformation** of two non-immunosuppressive **FK506** analogs when bound to FKBP by isotope-filtered NMR
AU Petros, Andrew M.; Kawai, Megumi; Luly, Jay R.; Fesik, Stephen W.
CS Pharm. Discovery Div., Abbot Lab., Abbot Park, IL, 60064, USA
SO FEBS Lett. (**1992**), 308(3), 309-14
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English
AB The **3D structure** of two unlabeled **FK506** analogs, (R)- and (S)-[18-OH]ascomycin, when bound to [U-13C,15N]FKBP were detd. by isotope-filtered 2D NMR expts. The **structures** for the R and S isomers that bind tightly to FKBP but lack immunosuppressive activity are compared to each other and to the **conformation** of the potent immunosuppressant, ascomycin, when bound to FKBP. The results are interpreted in terms of **calcineurin** binding at the FKBP/ascomycin complex.
IT **137951-12-3, Calcineurin**
RL: BIOL (Biological study)
(FKBP interaction with, **FK506** analogs inhibition of, **FK506** immunosuppression in relation to)
IT **104987-11-3, FK506**
RL: BIOL (Biological study)
(immunosuppression by, FKBP binding **conformation** in relation to)

L117 ANSWER 84 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:524022 HCAPLUS
DN 117:124022
TI Immunophilin structure: a template for immunosuppressive drug design?
AU Walkinshaw, M. D.; Kallen, J.; Weber, H. P.; Widmer, A.; Widmer, H.; Zurini, M.
CS Preclin. Res., Sandoz Pharma, Ltd., Basel, Switz.
SO Transplant. Proc. (**1992**), 24(4, Suppl. 2), 8-13
CODEN: TRPPA8; ISSN: 0041-1345
DT Journal
LA English
AB In answer to the question posed in the title, the authors can use the structures of immunophilins to rationalize the binding properties and, to some extent, the biol. properties of series of immunophilin ligands. The authors can further use the protein structures to design different ligands with modified binding (and pharmacol. and pharmacokinetic) properties. However, this is only half of the picture, the next step is to work toward detg. a **three-dimensional** picture of immunophilin ligand with the effector mol. (most probably **calcineurin**). This will enable one to suggest and design changes to the immunophilin ligands aimed at modulating both immunophilin binding and phosphatase activity. Structures of these multimeric complexes will also explain the puzzling overlap of function of FKBP and cyclophilin.

L117 ANSWER 85 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:252467 HCAPLUS
DN 116:252467
TI Motuporin, a potent protein phosphatase inhibitor isolated from the Papua New Guinea sponge Theonella swinhoei Gray
AU Dilip de Silva, E.; Williams, David E.; Andersen, Raymond J.; Klix, Heide; Holmes, Charles F. B.; Allen, Theresa M.
CS Dep. Chem., Univ. British Columbia, Vancouver, BC, V6T 1Z4, Can.
SO Tetrahedron Lett. (**1992**), 33(12), 1561-4
CODEN: TELEAY; ISSN: 0040-4039
DT Journal
LA English
GI



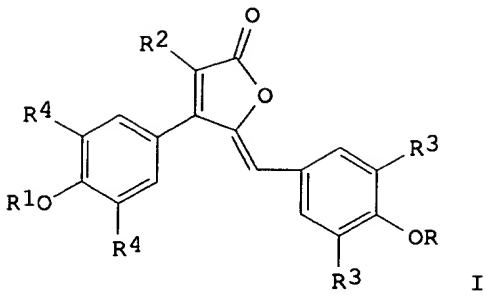
I

AB Motuporin (I), a cyclic pentapeptide that is a potent protein phosphatase-1 inhibitor and cytotoxin, was isolated from the marine sponge T. swinhoei collected in Papua, New Guinea. The structure of motuporin was elucidated by spectroscopic anal. and chem. degrdn.

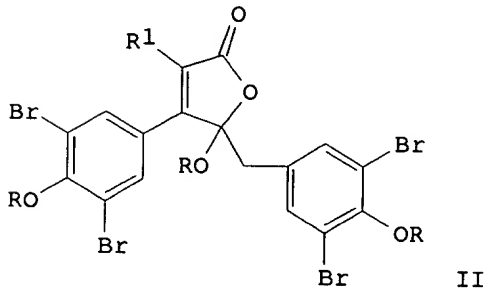
IT **9025-75-6**
RL: BIOL (Biological study)
(1, motuporin inhibition of)

L117 ANSWER 86 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1992:250158 HCAPLUS
DN 116:250158
TI Specific inhibition of **calcineurin** by type II synthetic pyrethroid insecticides
AU Enan, Essam; Matsumura, Fumio
CS Dep. Environ. Toxicol., Univ. California, Davis, CA, 95616, USA
SO Biochem. Pharmacol. (**1992**), 43(8), 1777-84
CODEN: BCPCA6; ISSN: 0006-2952
DT Journal
LA English
AB The inhibitory action of synthetic pyrethroids and some chlorinated hydrocarbon insecticides on the neutral calcium-calmodulin-dependent protein phosphatase, **calcineurin**, was studied using one radiotracer and two colorimetric methods. All insecticidal type II pyrethroids (cypermethrin, deltamethrin and fenvalerate) are potent inhibitors of isolated **calcineurin** from bovine brain. Their IC50 values were approx. 10-9 to 10-11M. By contrast, neither noninsecticidal chiral isomers of these pyrethroids, neuroactive Type I pyrethroids nor neuroactive chlorinated hydrocarbon insecticides showed comparable potencies against this enzyme. To confirm the action of Type II pyrethroid in situ, isolated intact rat brain synaptosomes were incubated with [32P]phosphoric acid and subsequently depolarized in the presence and absence of 0.1 .mu.M deltamethrin. As expected, there was a sharp rise in protein phosphorylation due to the action of **calcineurin**. Deltamethrin caused a distinct delay in the dephosphorylation process. The results clearly indicate that **calcineurin** is specifically inhibited by Type II pyrethroids.
IT **137951-12-3, Calcineurin**
RL: BIOL (Biological study)
(of brain, pyrethrins effect on)

L117 ANSWER 87 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:652335 HCAPLUS
DN 115:252335
TI Rubrolides A-H, metabolites of the colonial tunicate Ritterella rubra
AU Miao, Shichang; Andersen, Raymond J.
CS Dep. Chem., Univ. British Columbia, Vancouver, BC, V6T 1Z4, Can.
SO J. Org. Chem. (**1991**), 56(22), 6275-80
CODEN: JOCEAH; ISSN: 0022-3263
DT Journal
LA English
GI



I



II

AB Rubrolides A- (I; A: R = R1 = R2 = H, R3 = R4 = Br; B:R = R1 = H, R3 = R4 = Br, R2 = Cl; C: R = R = R1 = R4 = H. R3 = B; D: R = R1 = R2 = "!3 = H, R4 = Br; E: R = R1 = R3 = R4 = R2 = H; F: R = Me, R1 = R3 = R4 = R2 = H) and rubrolides G and H (II; G: R = R1 = H; H: R = H; H: R = H, R1 = CL), a new family of biol. active tunicate metabolites, were isolated from R. rubra. The structures of the rubrolides were solved by a combination of spectroscopic anal. and chem. interconversions. Rubrolides B and H represent some of the 1st chlorinated metabolites known from tunicates. The rubrolides are potent antibiotics and show moderate but selective inhibition of protein phosphatases 1 and 2A.

IT **9025-75-6**
RL: BIOL (Biological study)
(1 and 2A, inhibition of, by polyhalogenated hydrocarbons from tunicate)

L117 ANSWER 88 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:650055 HCAPLUS
DN 115:250055
TI Structure-function relationships of microcystins, liver tumor promoters, in interaction with protein phosphatase
AU Nishiwaki-Matsushima, Rie; Nishiwaki, Shinji; Ohta, Tetsuya; Yoshizawa, Seiji; Suganuma, Masami; Harada, Kenichi; Watanabe, Mariyo F.; Fujiki, Hirota
CS Cancer Prevent. Div., Natl. Cancer Cent. Res. Inst., Tokyo, 104, Japan
SO Jpn. J. Cancer Res. (**1991**), 82(9), 993-6
CODEN: JJCREP; ISSN: 0910-5050
DT Journal
LA English
AB Microcystins, isolated from toxic blue-green algae, are potent inhibitors of protein phosphatases 1 and 2A. Microcystin LR has a potent tumor-promoting activity on rat liver initiated with diethylnitrosamine. The structure of microcystins is unique in having an unusual amino acid, 3-amino-9-methoxy-10-phenyl-2,6,8-trimethyl-deca-4(E),6(E)-dienoic acid (Adda), which is thought to be significant for the activity. Geometrical isomers at C-7 in the Adda portion of microcystins, 6(Z)-Adda microcystins LR and RR, have been isolated from cyanobacteria. To est. their tumor-promoting activities and to understand the importance of the Adda portion for activity, the maternal microcystins LR and RR and their isomers were subjected to examn. of their interaction with protein phosphatases 1 and 2A and the release of glutamic pyruvic transaminase from rat liver. 6(Z)-Adda microcystins LR and RR bound to protein

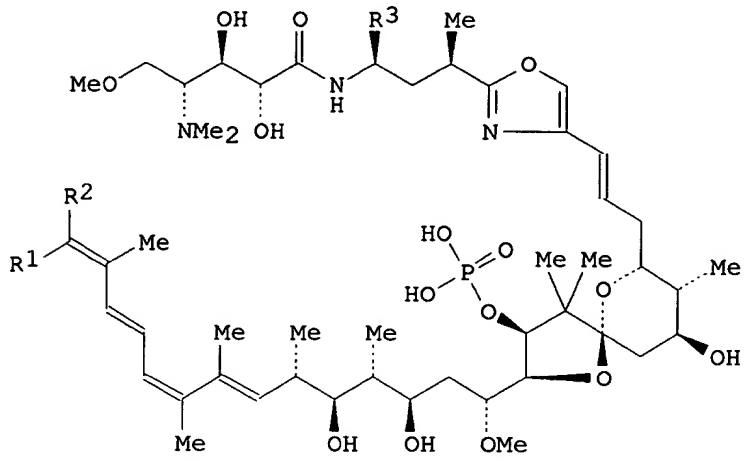
phosphatases 1 and 2A, inhibited their activities, and released glutamic pyruvic transaminase from rat liver into serum, ten to one hundred times more weakly than the maternal microcystins LR and RR. These results indicated that the conjugated diene with 4(E),6(E) geometry in the Adda portion is important in the interaction with protein phosphatases.

IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(1 and 2A, microcystins interaction with, liver carcinogenesis in relation to)

L117 ANSWER 89 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:577552 HCAPLUS
DN 115:177552
TI Signal convergence on protein kinase A as a molecular correlate of learning
AU Aszodi, Andras; Mueller, Uli; Friedrich, Peter; Spatz, Hanns Christof
CS Inst. Enzymol., Hung. Acad. Sci., Budapest, H-1113, Hung.
SO Proc. Natl. Acad. Sci. U. S. A. (**1991**), 88(13), 5832-6
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB The response of a reaction network composed of protein kinase A, calpain, and protein phosphatase to transient cAMP and Ca2+ signals was studied. An essential feature of signal convergence is that the regulatory subunit of cAMP-dissocd. protein kinase A undergoes limited proteolysis by the Ca2+-activated proteinase calpain. A dynamic model of this system based on kinetic differential equations was built and simulated by **computer**. The system shows analogies to typical features of associative learning such as acquisition, contiguity detection, extinction, and memory decay, suggesting that these biochem. reactions may be part of the mol. mechanism of learning in Drosophila.

IT **9025-75-6, Phosphoprotein phosphatase**
RL: BIOL (Biological study)
(calpain and protein kinase A and, interactions of, in mol. model for learning)

L117 ANSWER 90 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:468791 HCAPLUS
DN 115:68791
TI Calyculins E, F, G, and H, additional inhibitors of protein phosphatases 1 and 2A, from the marine sponge Discodermia calyx
AU Matsunaga, Shigeki; Fujiki, Hirota; Sakata, Daisuke; Fusetani, Nobuhiro
CS Res. Inst., Natl. Cancer Cent., Tokyo, 104, Japan
SO Tetrahedron (**1991**), 47(18-19), 2999-3006
CODEN: TETRAB; ISSN: 0040-4020
DT Journal
LA English
GI



I, R^1=CN, R^2=R^3=H

II, R^1=R^3=H, R^2=CN

III, R^1=CN, R^2=H, R^3=Me

IV, R^1=H, R^2=CN, R^3=Me

AB Calyculins E (I), F (II), G (III), and H (IV) were isolated from the marine sponge D. calyx. The structures for I-IV were assigned on the basis of the interpretation of spectral data. These novel calyculins were potent inhibitors of protein phosphatases 1 and 2A: EDs for 50% inhibition of protein phosphatases 2A activity by these calyculins were 2.7-6.0 nM.

IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(1 and 2A, calyculins of marine sponge as inhibitors of)

L117 ANSWER 91 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:76733 HCAPLUS
DN 114:76733
TI Structure-activity relationship within a series of okadaic acid derivatives
AU Nishiwaki, Shinji; Fujiki, Hirota; Suganuma, Masami; Furuya-Suguri, Hiroko; Matsushima, Rie; Iida, Yukari; Ojika, Makoto; Yamada, Kiyoyuki; Uemura, Daisuke; et al.
CS Cancer Prev. Div., Natl. Cancer Cent. Res. Inst., Tokyo, 104, Japan
SO Carcinogenesis (London) (**1990**), 11(10), 1837-41
CODEN: CRNGDP; ISSN: 0143-3334
DT Journal
LA English
AB Okadaic acid (OA; I) is a potent non-TPA-type tumor promoter on mouse skin. Seventeen OA derivs. were evaluated as possible tumor promoters by 3 tests: inhibition of specific [3H]OA binding to a particulate fraction of mouse skin contg. protein phosphatases, inhibition of protein phosphatase activity, and induction of ornithine decarboxylase in mouse skin. The carboxyl group as well as the four hydroxyl groups at C-2, C-7, C-24 and C-27 of OA are important for activity. Acanthifolicin, which gave pos. responses in these three biochem. tests as strong as those of OA and dinophysistoxin-1, is predicted to be an addnl. member of the OA class of tumor promoters.

IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(of brain, okadaic acid derivs. inhibition of, tumor promotion in relation to)

L117 ANSWER 92 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1991:38278 HCAPLUS
DN 114:38278

TI Synthetic peptide analogs of DARPP-32 (Mr 32,000 dopamine- and cAMP-regulated phosphoprotein), an inhibitor of protein phosphatase-1. Phosphorylation, dephosphorylation, and inhibitory activity
AU Hemmings, Hugh C., Jr.; Nairn, Angus C.; Elliott, James I.; Greengard, Paul
CS Lab. Mol. Cell. Neurosci., Rockefeller Univ., New York, NY, 10021-6399, USA
SO J. Biol. Chem. (**1990**), 265(33), 20369-76
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Synthetic peptides based on the threonine phosphorylation site and proposed inhibitory site of DARPP-32 (Mr = 32,000 as detd. by SDS-PAGE) were prepd. and analyzed as substrates for cAMP-dependent protein kinase and protein phosphatases-1c, -2Ac (the catalytic subunits of protein phosphatase-1 and 2A, resp.) and -2B, and as inhibitors of protein phosphatase-1c. Studies of the kinetics of phosphorylation of the peptides by cAMP-dependent protein kinase indicated an important role in facilitating phosphorylation for the region COOH-terminal to the phosphorylatable threonyl residue. Studies of the dephosphorylation of the phosphopeptides demonstrated that they were effectively dephosphorylated by protein phosphatase-2A and -2B and poorly dephosphorylated by protein phosphatase-1. The active inhibitory region of phospho-DARPP-32 was analyzed by measuring the effects of synthetic phosphopeptides on the activity of protein phosphatase-1c. Phospho-D32-(8-48) and phospho-D32-(8-38) inhibited protein phosphatase-1c with IC50 values of 2 .times. 10-8 and 4 .times. 10-8M, resp., compared with an IC50 of 8 .times. 10-9M for intact phospho-DARPP-32. Phospho-D32-(9-38) was equipotent with phospho-D32-(3-38); however, further NH2-terminal deletions resulted in marked redns. in IC50 values. An analog of an active DARPP-32 phosphopeptide contg. a phosphoseryl residue in place of the phosphothreonyl residue also exhibited a much reduced IC50. These data identify the essential inhibitory region of phospho-DARPP-32 as residues 9-38, which contains the phosphorylation site (threonine-34). This region exhibits extensive amino acid sequence identity with phosphatase inhibitor-1, a distinct inhibitor of protein phosphatase-1. Kinetic studies of the inhibition of protein phosphatase-1c by phospho-D32-(9-38), a potent inhibitor, as well as by phospho-D32-(10-38), a weak inhibitor, indicated a mixed competitive/noncompetitive mechanism of inhibition, as has been previously found for both intact phospho-DARPP-32 and intact phospho-inhibitor-1. These findings support the hypothesis that a 30-amino acid domain in the NH2-terminal region of phospho-DARPP-32 is sufficient for the inhibition of protein phosphatase-1.
IT **9025-75-6, Phosphoprotein phosphatase**
RL: BIOL (Biological study)
(-1c, phosphoprotein DARPP-32 inhibitory domain for, identification of and inhibitor-1 sequence homol. with)

L117 ANSWER 93 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:626148 HCAPLUS
DN 113:226148
TI Inhibition of protein phosphatases-1 and -2A with acanthifolicin. Comparison with diarrhetic shellfish toxins and identification of a region on okadaic acid important for phosphatase inhibition
AU Holmes, Charles F. B.; Luu, Hue A.; Carrier, France; Schmitz, Francis J.
CS Biotechnol. Res. Inst., Natl. Res. Counc., Montreal, PQ, H4P 2R2, Can.
SO FEBS Lett. (**1990**), 270(1-2), 216-18
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English
AB Acanthifolicin (9,10-epithio-okadaic acid from Pandoras acanthifolium) inhibited protein phosphatase-1 (PP1) similarly to okadaic acid (IC50 = 20 nM and 19 nM, resp.) but was slightly less active against protein phosphatase-2A (PP2A) (IC50 = 1 nM and 0.2 nM, resp.). Me esterification of acanthifolicin sharply reduced its activity. PP2A was inhibited with

an IC50 = 5.0 .mu.M, while PP1 was inhibited <10% at 250 .mu.M toxin. Okadaic acid Me ester was similarly inactive whereas dinophysistoxin-1 (35-Me okadaic acid) inhibited PP1/2A almost as potently as okadaic acid. Pure acanthifolicin/okadaic acid Me ester may be useful as specific inhibitors of PP2A at 1-10 .mu.M concns. in vitro and perhaps in vivo. The data also indicate that a region on these toxins important for PP1/2A inhibition comprises the single carboxyl group.

IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(1 and 2A, acanthifolicin and okadaic acid and their derivs. inhibition of)

L117 ANSWER 94 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:231742 HCAPLUS
DN 112:231742
TI Synthetic peptides as model substrates for the study of the specificity of the polycation-stimulated protein phosphatases
AU Agostinis, Patrizia; Goris, Jozef; Pinna, Lorenzo A.; Marchiori, Fernando; Perich, John W.; Meyer, Helmut E.; Merlevede, Wilfried
CS Fac. Geneeskd., Kathol. Univ. Leuven, Louvain, B-3000, Belg.
SO Eur. J. Biochem. (**1990**), 189(2), 235-41
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB The substrate specificity of the different forms of the polycation-stimulated (PCS, type 2A) **phosphoprotein phosphatases** and of the active catalytic subunit of the ATP,Mg-dependent (type 1) phosphatase (AMDC) was investigated using synthetic peptides phosphorylated by either cAMP-dependent protein kinase or by casein kinase-2. The PCS phosphatases were very efficient toward the phosphothreonine [Thr(P)] peptides, RRAT(P)VA and RRREEET(P)EEE, when compared with the phosphoserine [Ser(P)] analogs, RRAS(P)VA and RRREEES(P)EEEAA. Despite their distinct sequence, both Thr(P) peptides were excellent substrates for the PCSM and PCSH1 phosphatases, being dephosphorylated faster than phosphorylase a. The slow dephosphorylation of RRAS(P)VA by the PCS phosphatases could be increased substantially by the insertion of N-terminal (arginine) basic residues. In contrast with the latter, the AMDC phosphatase showed very poor activity toward all phosphopeptides tested, without preference for either Ser(P) or Thr(P) peptides. However, N-terminal basic residues also favored the dephosphorylation of otherwise almost inert substrates by the AMDC phosphatase. Hence, whereas the dephosphorylation of Thr(P) substrates by the PCS phosphatases is highly favored by the nature of the phosphorylated amino acid, phosphatase activity toward Ser(P)-contg. peptides may require specific determinants in the primary structure of the phosphorylation site.

IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(polycation-stimulated, substrate specificity of, for synthetic phosphopeptides)

L117 ANSWER 95 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1990:74541 HCAPLUS
DN 112:74541
TI A mechanism for the Hebb and the anti-Hebb processes underlying learning and memory
AU Lisman, John
CS Dep. Biol., Brandeis Univ., Waltham, MA, 02254, USA
SO Proc. Natl. Acad. Sci. U. S. A. (**1989**), 86(23), 9574-8
CODEN: PNASA6; ISSN: 0027-8424
DT Journal
LA English
AB In a previous paper (Lisman, J.E.; Goldring, M.A., 1988), a model was presented showing how the group of Ca2+/calmodulin-dependent protein kinase II mols. contained within a postsynaptic d. could stably store a graded synaptic wt. This paper completes the model by showing how

bidirectional control of synaptic wt. could be achieved. It is proposed that the quant. level of the activity-dependent rise in postsynaptic Ca2+ dets. whether the synaptic wt. will increase or decrease. It is further proposed that redn. of synaptic wt. is governed by protein phosphatase 1, an enzyme indirectly controlled by Ca2+ through reactions involving phosphatase inhibitor 1, cAMP-dependent protein kinase, **calcineurin**, and adenylate cyclase. Modeling of this biochem. system shows that it can function as an analog **computer** that can store a synaptic wt. and modify it in accord with the Hebb and anti-Hebb learning rules.

IT **9025-75-6**
RL: BIOL (Biological study)
(1 and inhibitor 1, in Hebb and anti-Hebb process regulation in learning and memory)

L117 ANSWER 96 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1989:512615 HCAPLUS
DN 111:112615
TI The dephosphorylation of lens .alpha.-**crystallin** A chain
AU Chiesa, Raul; Spector, Abraham
CS Coll. Physicians Surg., Columbia Univ., New York, NY, 10032, USA
SO Biochem. Biophys. Res. Commun. (**1989**), 162(3), 1494-501
CODEN: BBRCA9; ISSN: 0006-291X
DT Journal
LA English
AB The presence of a **phosphoprotein phosphatase** activity is reported in bovine lens prepns. which dephosphorylates .alpha.Ap, the phosphorylated form of .alpha.A, one of the .alpha.-**crystallin** polypeptides, in a Ca2+/calmodulin-dependent manner. The activity was found in sol. prepns. from epithelial cells, but it could not be detected in similar prepns. from fiber cells. A 60,000-Mr calmodulin-binding polypeptide and a 15,000-Mr polypeptide found in the epithelial cell prepns. comigrated in SDS-PAGE with the A and B subunits of bovine brain **calcineurin** (**phosphoprotein phosphatase** 2B), resp. The 15,000-Mr polypeptide was specifically recognized by an anti-bovine brain **calcineurin** antiserum. Bovine brain **calcineurin** was as effective in dephosphorylating .alpha.Ap as the lens prepns. Thus, it is likely that the activity present in the lens is related to this enzyme. Apparently, the lens specific polypeptide .alpha.A may be subject to metabolic control through phosphorylation and dephosphorylation pathways regulated by cAMP and Ca, resp. Changes in the activities of these pathways appear to occur during differentiation of the lens epithelial cell and may be related to gene regulation during the differentiation process.

IT **9025-75-6, Phosphoprotein phosphatase**
RL: BIOL (Biological study)
(of eye lens, .alpha.-**crystallin** A chain dephosphorylation by)

L117 ANSWER 97 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1989:452846 HCAPLUS
DN 111:52846
TI Molecular basis for protein dephosphorylation. A study with phosphorylated peptide substrates
AU Pinna, Lorenzo A.; Agostinis, Patrizia; Donella-Deana, Arianna; Marchiori, Fernando
CS Dip. Chim. Biol. Chim. Org., Univ. Padova, Padua, Italy
SO Adv. Protein Phosphatases (**1989**), 5, 51-74
CODEN: APPHE3
DT Journal; General Review
LA English
AB A review with 53 refs. on the mol. basis of the specificity of **phosphoprotein phosphatases** as studied with phosphosylated peptide substrates. Peptide structural features and different phosphatase specificities are considered.

IT **9025-75-6, Phosphoprotein phosphatase**

RL: BIOL (Biological study)
(specificity of, mol. basis of)

L117 ANSWER 98 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1989:437121 HCAPLUS
DN 111:37121
TI A quantitative model for the kinetics of cAMP-dependent protein kinase (type II) activity. Long-term activation of the kinase and its possible relevance to learning and memory
AU Buxbaum, Joseph Daniel; Dudai, Yadin
CS Dep. Neurobiol., Weizmann Inst. Sci., Rehovot, 76100, Israel
SO J. Biol. Chem. (**1989**), 264(16), 9344-51
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Using **computer** simulation, the kinetics of cAMP-dependent protein kinase, type II, following transient pulses of cAMP were modeled. Under the appropriate physiol. conditions, the kinase can remain activated .ltoreq.20 min after the cessation of adenylate cyclase activation, in a process termed long-term activation. Long-term activation depends in part on the state of phosphorylation of the regulatory subunit, because phosphorylation of the regulatory subunit regulates the affinity of this subunit for the catalytic subunit. The model was used to simulate expts. that have been performed on the kinetic and steady-state activities of cAMP-dependent protein kinase and good agreement was found between the simulations and the exptl. data. The effects of the activity of phosphodiesterase, adenylate cyclase, and protein phosphatase on the kinetics of cAMP-dependent protein kinase have been modeled, as have the effects of different ratios of regulatory subunit to catalytic subunit. The activation of the cAMP-dependent protein kinase in Drosophila learning and memory mutants having primary or secondary defects in the cAMP cascade was also simulated. Predictions are made regarding the behavior of different mutants, which are in line with the exptl. data. The model corroborates the assumption that the cAMP cascade may play a role in learning and short-term memory.
IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(protein kinase regulation by, in learning and memory, model for)

L117 ANSWER 99 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1989:403151 HCAPLUS
DN 111:3151
TI Structural basis for the specificity of protein phosphorylation and dephosphorylation processes
AU Pinna, Lorenzo A.
CS Ist. Chim. Biol., Univ. Padova, Padua, 35131, Italy
SO Adv. Exp. Med. Biol. (**1988**), 231(Adv. Post-Transl. Modif. Proteins Aging), 433-43
CODEN: AEMBAP; ISSN: 0065-2598
DT Journal; General Review
LA English
AB The phosphorylation of synthetic peptides by tyrosine kinases I, IIB, and III of spleen were compared. Apparently, the kinases displayed a preference for residues located downstream from the acidic amino acids while each kinase showed variable specificity. Included with the data is a review on structural requirements for protein kinases and structural factors influencing dephosphorylation by protein phosphatases.
IT **9025-75-6**, Protein phosphatase
RL: BIOL (Biological study)
(protein dephosphorylation by, structural factors in)

L117 ANSWER 100 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:584563 HCAPLUS
DN 109:184563
TI Segments of bacteriophage .lambda. (orf221) and .vphi.80 are homologous to genes coding for mammalian protein phosphatases

AU Cohen, Patricia T. W.; Collins, John F.; Coulson, Andrew F. W.; Berndt, Norbert; Da Cruz e Silva, Odete B.
CS Dep. Biochem., Univ. Dundee, Dundee, DD1 4HN, UK
SO Gene (**1988**), 69(1), 131-4
CODEN: GENED6; ISSN: 0378-1119
DT Journal
LA English
AB The amino acid sequences of mammalian protein phosphatase 1 and 2A were compared pairwise with every sequence in the National Biomedical Research Foundation protein sequence **database** using an exhaustive searching program. The N-terminal half of the protein encoded by an open reading frame, orf221, in phage .lambda. (nt 43,224-43,886 in the map of Daniels D. L., et al., 1983) shows 35% identity to either protein phosphatase I or 2A in this region. If conservative replacements are included, the overall homol. rises to 49%. A gene in .vphi.80 also shows 35% identity with the mammalian protein phosphatases. Thus, orf221 of phage .lambda. and the homologous .vphi.80 gene may encode protein phosphatases. The possible roles of protein phosphorylation in the propagation of phage are discussed.
IT **9025-75-6**, Protein phosphatase
RL: PRP (Properties)
(1 and 2A, mammalian gene for, phage .lambda. and .vphi.80 genes homol. to)

L117 ANSWER 101 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:566242 HCAPLUS
DN 109:166242
TI Functional significance of the central helix in calmodulin
AU Putkey, John A.; Ono, Tomio; VanBerkum, Mark F. A.; Means, Anthony R.
CS Dep. Cell Biol., Baylor Coll. Med., Houston, TX, 77030, USA
SO J. Biol. Chem. (**1988**), 263(23), 11242-9
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The 3-.ANG. **crystal** structure of calmodulin indicates that it has a polarized tertiary arrangement in which Ca binding domains I and II are sepd. from domains III and IV by a long central helix consisting of residues 65-92. To investigate the functional significance of the central helix, mutated calmodulins were engineered with alterations in this region. Using oligonucleotide-primed site-directed mutagenesis, threonine (Thr)-79 was converted to proline (Pro)-79 to generate CaMPM. CaMPM was further mutated by insertion of Pro-Ser-Thr-Asp between aspartate (Asp)-78 and Pro-79 to yield CaMIM. Calmodulin, CaMPM, and CaMIM were indistinguishable in their ability to activate **calcineurin** and Ca2+-ATPase. All mutated calmodulins would also maximally activate cGMP-phosphodiesterase and myosin light-chain kinase, however, the concns. of CaMPM and CaMIM necessary for half-maximal activation (Kact) were 2- and 9-fold greater, resp., than CaM23. Conversion of the 2 Pro residues in CaMIM to amino acids that predict retention of helical secondary structure did not restore normal calmodulin activity. To investigate the nature of the interaction between mutated calmodulins and target enzymes, synthetic peptides modeled after the calmodulin binding region of smooth and skeletal muscle myosin light-chain kinase were prepd. and used as inhibitors of calmodulin-dependent cGMP phosphodiesterase. The data suggest that the different kinetics of activation of myosin light-chain kinase by CaM23 and CaMIM are not due to differences in the ability of the activators to bind to the calmodulin binding site of this enzyme. These observations are consistent with a model in which the length but not compn. of the central helix is more important for the activation of certain enzymes. The data also support the hypothesis that calmodulin contains multiple sites for protein-protein interaction that are differentially recognized by its multiple target proteins.

L117 ANSWER 102 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1988:452374 HCAPLUS
DN 109:52374

TI Kinetics of protein phosphorylation in microvessels isolated from rat brain: modulation by second messengers
AU Olah, Z.; Novak, R.; Lengyel, I.; Dux, E.; Joo, F.
CS Food Ind. Coll., Univ. Hortic., Szeged, Hung.
SO J. Neurochem. (**1988**), 51(1), 49-56
CODEN: JONRA9; ISSN: 0022-3042
DT Journal
LA English
AB The role of 2nd messengers in the regulation of protein phosphorylation was studied in microvessels isolated from rat cerebral cortex. The phosphoproteins were sepd. by SDS-PAGE, and the kinetics of 32P incorporation into specific protein substrates were evaluated by **computer**-aided, x-ray film densitometry. With the use of this method, Ca2+-calmodulin (CAM)-, Ca2+/phospholipid (PK C)-, cGMP-, and cAMP-dependent protein kinases were detected. CAM-dependent protein kinase proved to be the major phosphorylating enzyme in the microvascular fraction of the rat cerebral cortex; the activity of cGMP-dependent protein kinase was much higher than that of the cAMP-dependent one. Autophosphorylation of both the .alpha.- and .beta.-subunits of CAM-dependent protein kinase and the proteolytic fragment of the PK C enzyme was also detected. The kinetics of phosphorylation of the individual polypeptides indicate the presence in the cerebral endothelium of **phosphoprotein phosphatases**. The phosphorylation of proteins in the cerebral capillaries was more or less reversible; the addn. of 2nd messengers initiated a very rapid increase in 32P incorporation, followed by a slow decrease. Because the intracellular signal transducers like Ca2+ and cyclic nucleotides are frequently regulated by different vasoactive substances in the endothelial cells, the modified phosphorylation evoked by these 2nd messengers may be related in vivo to certain changes in the transport processes of the blood-brain barrier.
IT **9025-75-6, Phosphoprotein phosphatase**
RL: BIOL (Biological study)
(of brain microvessel endothelium, protein phosphorylation in relation to)

L117 ANSWER 103 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:550086 HCAPLUS
DN 107:150086
TI Cytochrome P-450 cholesterol 7.alpha.-hydroxylase: inhibition of enzyme deactivation by structurally diverse calmodulin antagonists and phosphatase inhibitors
AU Holsztynska, Elzbieta; Waxman, David J.
CS Dana-Farber Cancer Inst., Harvard Med. Sch., Boston, MA, 02115, USA
SO Arch. Biochem. Biophys. (**1987**), 256(2), 543-59
CODEN: ABBIA4; ISSN: 0003-9861
DT Journal
LA English
AB Cytochrome P 450-contg. cholesterol 7.alpha.-hydroxylase (I) catalyzes the 1st and rate-limiting step in the conversion of cholesterol to bile acids. Incubation of rat liver microsomes in 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid buffer resulted in a time-dependent deactivation of I which was markedly accelerated by the nonionic detergent, Tween 80. Microsomal NADPH-cytochrome P 450 reductase and cytochrome P 450-dependent 7-ethoxycoumarin O-deethylase activities were unaffected under these conditions, evidencing the selectivity of the deactivation process for I. The rate (t1/2 = 15-19 min at 37.degree.) and maximal extent of I deactivation (.gtoreq.90%) were both unaffected by the presence of cytosolic proteins and were also not dependent on the initial enzyme level, as shown using liver microsomes isolated from untreated, cholestyramine-fed, and xenobiotic-induced rats exhibiting an 8-fold range in I activity. Scavengers for reduced O species were also without effect. I was stabilized some 6-7-fold (t1/2 = 94-143 min) by the phosphatase inhibitor, NaF. Of a series of other phosphatase inhibitors examd., including, among others, EDTA, vanadate, and molybdate, only phosphate-contg. compds. and the calmodulin antagonist, trifluoperazine,

an inhibitor of the Ca2+-calmodulin-dependent **phosphoprotein phosphatase, calcineurin**, effectively stabilized I. The modulation of I deactivation by these inhibitors generally paralleled their effects on isolated **calcineurin**. A variety of structurally diverse calmodulin antagonists examd. also effectively protected I from deactivation; these included calmidazolium and tamoxifen, chlorpromazine, thioridazine, amitriptyline, imipramine, and the naphthalenesulfonamide compd. W-7. Structure-activity anal. of several phenothiazines and their derivs. indicated that although little activity was exhibited by the sulfoxides, some protection was provided by the corresponding sulfones. On the basis of these observations, various models for the mol. basis of enzyme deactivation are considered, including the hypothesis that a **calcineurin**-like microsomal **phosphoprotein phosphatase** mediates deactivation of I.

IT **9025-75-6**
RL: BIOL (Biological study)
(inhibitors of, cholesterol hydroxylase deactivation inhibition by)

L117 ANSWER 104 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:492599 HCAPLUS
DN 107:92599
TI Calcium- and calmodulin-sensitive interactions of **calcineurin** with phospholipids
AU Politino, Michael; King, Marita M.
CS Dep. Chem., Ohio State Univ., Columbus, OH, 43210, USA
SO J. Biol. Chem. (**1987**), 262(21), 10109-13
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Phys. assocn. of **calcineurin** with phosphatidylserine (PS) or phosphatidylglycerol (PG) was obsd. by mol. exclusion chromatog.; the enzyme did not assoc. with phosphatidylethanolamine or phosphatidylcholine. The interactions with PS and PG were enhanced by Ca2+, which implicates a regulatory role for the Ca2+-binding subunit in this process. Addn. of PG or PS to std. **calcineurin** assays elicited profound changes in enzymic activity; phosphatidylcholine and phosphatidylethanolamine were without effect. Up to 23-fold stimulation of the calmodulin-independent activity was obsd. with phosphorylated histone H1 or synapsin I as the substrates. In contrast, the activity toward p-nitrophenyl phosphate and tyrosine phosphate was found to be inhibited. A characterization and comparison of the 2 opposite responses showed that: (1) the phospholipids had insignificant effects on the Km for substrates, (2) the phospholipid specificity for activation and inhibition was nearly indistinguishable, half-maximal activation and inhibition were obtained (3) at similar concns. of PG (K0.5 = 0.21 and 0.14 mg/mL, resp.), and (4) calmodulin enhanced the responses to PG (K0.5 = 0.064 and 0.033 mg/mL for activation and inhibition, resp.) to similar extents. Together, these observations demonstrate that the 2 substrate-dependent responses of **calcineurin** are due to the assocn. of the phosphatase with phospholipids and not a result of substrate-phospholipid interactions. This suggests that Ca2+- and calmodulin-stimulated interactions of **calcineurin** with acidic phospholipids may play a role in regulating the substrate specificity of this multifunctional phosphatase.

L117 ANSWER 105 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1987:134205 HCAPLUS
DN 106:134205
TI Dephosphorylation of phosphoproteins and synthetic phosphopeptides. Study of the specificity of the polycation-stimulated and magnesium ATP-dependent phosphorylase phosphatases
AU Agostinis, Patrizia; Goris, Jozef; Waelkens, Etienne; Pinna, Lorenzo A.; Marchiori, Fernando; Merlevede, Wilfried
CS Fac. Geneeskd., Kathol. Univ. Leuven, Louvain, Belg.
SO J. Biol. Chem. (**1987**), 262(3), 1060-4
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal

LA English
AB The substrate specificity of different forms of polycation-stimulated (PCSH, PCSL, and PCSC) phosphorylase phosphatases and of the catalytic subunit of the MgATP-dependent protein phosphatase from rabbit skeletal muscle was investigated. This was done, with phosphorylase a as the ref. substrate, by using the synthetic phosphopeptides patterned after the phosphorylated sites of pyruvate kinase (type L) (Arg2-Ala-[32P]Ser-Val-Ala (S2), and its [32P]threonine substitute (T4)), inhibitor-1 (Arg4-Pro-[32P]Thr-Pro-Ala (T5), Arg2-Pro-[32P]Thr-Pro-Ala (T1), and its [32P]serine substitute (S1)), and some modified phosphopeptides (Arg2-Ala-[32P]Thr-Pro-Ala (T2) and Arg2-Pro-[32P]Thr-Val-Ala (T3)), all phosphorylated by cAMP-dependent protein kinase. In addn., casein([32P]Thr), phosphorylated by casein kinase-2, was also tested. The PCS phosphatases show a striking preference for the T4 configuration, PCSC being the least efficient. The catalytic subunit of the MgATP-dependent phosphatase was almost completely inactive toward all these substrates. As shown for the PCSH phosphatase, and comparing with T4, the 2 proline residues flanking the Thr(P) in T1 and T5, as in inhibitor-1, drastically impaired the dephosphorylation by lowering the Vmax and not by affecting the apparent Km. The C-terminal proline (as in T2) by itself represents a highly unfavorable factor in the dephosphorylation. The crit. effect of the sequence X-Thr(P)-Pro (where X is an amino acid residue) or Pro-Thr(P)-Pro (T1, T2, T5, and inhibitor-1) can be overcome by Mn2+. The addnl. finding that this is not the case with the Pro-Ser(P)-Pro sequence (S1) suggests that the effect of Mn2+ is highly substrate specific. These observations show the considerable importance of the primary structure of the substrate in detg. the specificity of the protein phosphatases.
IT **9025-75-6, Phosphoprotein phosphatase**
RL: BIOL (Biological study)
(magnesium ATP-dependent, substrate specificity of)

L117 ANSWER 106 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:623289 HCAPLUS
DN 105:223289
TI Presence of a magnesium-ATP/ADP-dependent pp50 phosphatase in bovine brain coated vesicles
AU Pauloin, Alain; Jolles, Pierre
CS Lab. Proteines, Univ. Paris V, Paris, F 75270, Fr.
SO J. Biol. Chem. (**1986**), 261(27), 12568-73
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Bovine brain coated vesicles contain an enzyme which dephosphorylates pp50 (an unique, 50-kilodalton coated vesicle integral protein). This **phosphoprotein phosphatase** occurs under 2 interconvertible active and inactive forms. The activation process needs the simultaneous presence of Mg2+ and ATP or ADP. Unchelated ATP, but not unchelated ADP, inactivates the pp50 phosphatase. The latter is assocd. with the vesicular core. MgADP activation of the pp50 phosphatase implicates a different mechanism which does not need a phosphorylated intermediate. Thus, the pp50 phosphatase might belong to a new phosphatase type distinct from the 4 other classes of well known protein phosphatases.

L117 ANSWER 107 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:493370 HCAPLUS
DN 105:93370
TI Purification, subunit composition and regulatory properties of the ATP.cntdot.magnesium-dependent form of type I **phosphoprotein phosphatase** from bovine heart
AU Price, Daniel J.; Tabarini, Diane; Li, Heng Chun
CS Mount Sinai Sch. Med., City Univ. New York, New York, NY, 10029, USA
SO Eur. J. Biochem. (**1986**), 158(3), 635-45
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English

AB The ATP.cntdot.Mg-dependent **phosphoprotein phosphatase** was purified from bovine heart to near homogeneity. It is a heterodimer [75 kilodaltons (kDa)] consisting of a catalytic (C) subunit (40 kDa) and a regulatory (R) subunit (35 kDa). The R subunit, which is identical to inhibitor-2, is transiently phosphorylated during activation of the enzyme catalyzed by phosphatase-1 kinase (FA). Maximal activation requires preincubation of the phosphatase with FA and ATP.cntdot.Mg. However, relatively low yet definitively demonstrable basal activity can be expressed by Mg2+ alone (ranging from 3-10% of the FA.cntdot.ATP.cntdot.Mg activity, depending on the degree of endogenous proteolytic damage of the phosphatase during purifn.), but not by either FA or ATP alone. Limited trypsinization results in a rapid and total degrdn. of the R subunit and partial degrdn. of the 40-kDa C subunit to active proteins of 35-38 kDa. The resulting nicked C subunit of 35-38 kDa is no longer dependent on FA for activation and can be fully activated by Mg2+ (or Mn2+) alone. Endogenous proteolytic damage of the R subunit also results in an increase of activity that can be expressed by the metals alone, with a concomitant decrease of the FA-dependent activation. Although Mn2+ is slightly more effective than Mg2+ in expressing the holoenzyme basal activity, the activation by Mn2+ is only .apprx.60% of that of Mg2+ when FA and ATP are also present. In the activation by adenosine 5'-{.gamma.-thiotriphosphate (ATP[.gamma.S])}, Co2+ is the most effective cofactor. The activation by ATP[.gamma.S].cntdot.Co2+ is >50% of that by ATP.cntdot.Mg. Thus, Mg2+ is the natural divalent cation for the FA-catalyzed activation in which Mg2+ plays 2 distinctly different roles: (1) it forms Mg.cntdot.ATP, which serves as a substrate for the kinase, and (2) it acts as an essential cofactor for the catalytic function of the phosphatase. The discrepancies between the results obtained by this and other labs. with respect to the effectiveness of Mg2+ and ATP[.gamma.S] in the activation of the phosphatase are discussed.

IT **9025-75-6P**
RL: PREP (Preparation)
(magnesium-ATP-dependent, I, of heart, purifn. and subunit compn. and regulatory properties of)

L117 ANSWER 108 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:456979 HCAPLUS
DN 105:56979
TI Subunit structure and properties of the glycogen-bound **phosphoprotein phosphatase** from skeletal muscle
AU Khatra, Balwant S.
CS Sch. Med., Vanderbilt Univ., Nashville, TN, 37232, USA
SO J. Biol. Chem. (**1986**), 261(19), 8944-52
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB A high-mol.-wt. **phosphoprotein phosphatase** (I) was purified .apprx.11,000-fold from the glycogen-protein complex of rabbit skeletal muscle. PAGE of the prepn. in the absence of SDS showed a major protein band which contained the I activity. SDS-PAGE also showed a major protein band migrating at 38,000 daltons. The sedimentation coeff., Stokes' radius, and frictional ratio of I were 4.4 S, 4.4 nm, and 1.53, resp. Based on these values, the mol. wt. of I was calcd. to be 83,000. The high-mol.-wt. I was dissocd. upon chromatog. on a reactive red-120 agarose column. The sedimentation coeff., Stokes' radius, and frictional ratio of the dissocd. enzyme (termed monomer) were 4.1 S, 2.4 nm, and 1.05, resp. The mol. wt. of the monomer enzyme was 38,000 by PAGE. Incubation of high-mol.-wt. I with a cleavable crosslinking reagent 3,3'-dithiobis(sulfosuccinimidyl propionate), resulted in formation of a crosslinked complex. The mol. wt. of the crosslinked complex was 85,000 and 2nd dimension gel electrophoresis of the cleaved crosslinked complex showed that the latter contained only 38,000-dalton bands. Limited trypsinization of the enzyme released a .apprx.4000-dalton peptide from the monomers and dissocd. high-mol.-wt. I into 34,000-dalton monomers. Thus, the catalytic activity of native glycogen-bound I appears to reside in a dimer of 38,000-dalton subunits.

IT **9025-75-6**
RL: BIOL (Biological study)
(glycogen-bound, of muscle, subunit structure and properties of)

L117 ANSWER 109 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:221179 HCAPLUS
DN 104:221179
TI Purification and characterization of two inactive/latent protein phosphatases from pig brain
AU Yang, Shiaw Der; Yu, Jau Song; Fong, Yiu Lian
CS Inst. Life Sci., Natl. Tsing Hua Univ., Hsinchu, 30043, Taiwan
SO J. Biol. Chem. (**1986**), 261(12), 5590-6
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Two inactive/latent **phosphoprotein phosphatases** termed LP-1 (mol. wt. = 260,000) and LP-2 (mol. wt. = 350,000) were identified and purified from pig brain. Examn. of **mol. structures** indicated that LP-1 has 3 subunits with mol. wts. of 69,000, 55,000, and 34,000, resp., whereas LP-2 contains only 1 subunit, with a mol. wt. of 49,000. When using phosphorylase a as a substrate, LP-1 was completely inactive and could be dramatically activated by freezing and thawing in 0.2M 2-mercaptoethanol, whereas LP-2 contained some basal activity but could also be stimulated 40-fold by the same treatment. Kinetic anal. further indicated that both LP-1 and LP-2 enzymes dephosphorylate histone 2A, myelin basic protein, and phosphorylase a at a rather comparable rate, but the dephosphorylation of histone 2A and myelin basic protein appears to be spontaneously active. This, together with the results that trypsinolysis could specifically knock off phosphorylase phosphatase activity but caused no effect on the assocd. myelin basic protein/histone phosphatase activities, supports the notion that a 2-site mechanism may possibly be involved in the regulation of substrate specificity of LP-1 and LP-2 enzymes in the central nervous system.
IT **9025-75-6P**
RL: PREP (Preparation)
(latent forms LP-1 and LP-2 of, of brain, purifn. and properties of)

L117 ANSWER 110 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:202863 HCAPLUS
DN 104:202863
TI The role of substrate structure in recognition and regulation of enzymic interconversion of proteins
AU Martensen, Todd M.
CS Lab. Biochem., Natl. Heart, Lung, Blood Inst., Bethesda, MD, 20205, USA
SO Curr. Top. Cell. Regul. (**1985**), 27(Modulation Covalent Modif.), 171-81
CODEN: CTCRAE; ISSN: 0070-2137
DT Journal
LA English
AB A discussion of the substrate conformational and(or) quaternary structural requirements of enzymes involved in the post-translational covalent modification of proteins is presented. Specific examples discussed are (1) the hydrolysis of the phosphodiester bond of adenylylated glutamine synthetase by micrococcal nuclease and by snake venom endonuclease, and (2) the phosphorylation-dephosphorylation of phosphorylase by phosphorylase kinase and **phosphoprotein phosphatase**, resp.
IT **9025-75-6**
RL: BIOL (Biological study)
(phosphorylase dephosphorylation by, substrate structural requirements for)

L117 ANSWER 111 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:182391 HCAPLUS
DN 104:182391
TI Modification of the calmodulin-stimulated phosphatase, **calcineurin**

, by sulfhydryl reagents
AU King, Marita M.
CS Dep. Chem., Ohio State Univ., Columbus, OH, 43210, USA
SO J. Biol. Chem. (**1986**), 261(9), 4081-4
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB The importance of cysteine residues on the function and regulation of **calcineurin** was investigated by using chem. modification by SH reagents. **Calcineurin** was stable toward incubation with several commonly employed reagents but not toward p-hydroxymercuribenzoic acid and N-ethylmaleimide (NEM), both of which partially inactivated the Ca2+-supported activity and rapidly abolished its activation by Ni2+. Ni2+ provided only slight protection from inactivation by NEM, which argued against labeling of the Ni2+-binding site(s). In contrast, protection was provided by Ca2+; this is probably due to allosteric effects, since Ca2+ binds to the B subunit, whereas the A subunit contains all of the cysteine residues of **calcineurin**. Activation of **calcineurin** by Ni2+ is thus apparently synergistic with Ca2+ and indicates an important role for the Ca2+-binding subunit in the activation process. Labeling of **calcineurin** by [14C]NEM was biphasic. An initial, rapid phase was without effect on the Ni2+ activity; inactivation correlated with a 2nd, slower phase of modification. Differential labeling in the presence and absence of Ca2+ suggested that inactivation correlates with labeling of 2 residues. A kinetic anal. of the reaction order indicated that modification of only 1 of these groups may be responsible for inactivation; thus, 1 cysteine residue on the catalytic subunit appears to be important in establishing the Ni2+-activated conformation of **calcineurin**.

L117 ANSWER 112 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1986:144558 HCAPLUS
DN 104:144558
TI Limited proteolytic digestion and dissociation of smooth muscle phosphatase-I modifies its substrate specificity. Preparation and properties of different forms of smooth muscle phosphatase-I
AU Pato, Mary D.; Kerc, Ewa
CS Dep. Biochem., Univ. Saskatchewan, Saskatoon, SK, S7N 0W0, Can.
SO J. Biol. Chem. (**1986**), 261(8), 3770-4
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Smooth muscle **phosphoprotein phosphatase**-I (I), purified from turkey gizzard smooth muscle, is composed of 2 regulatory subunits (mol. wt. = 60,000 and 55,000) and a catalytic subunit (mol. wt. = 38,000). Two other forms of I were also prepd. and characterized. The free catalytic subunit, termed Ic, was prepd. by EtOH treatment of I, and a form devoid of the 55,000-dalton (Da) subunit, termed I2, was prepd. by limited tryptic digestion. Exposure of I proteinases like trypsin and chymotrypsin resulted in a rapid degrdn. of the 55,000-Da polypeptide. Degrdn. of Ic was obsd. only upon prolonged digestion. The 60,000-Da polypeptide appeared to be resistant to both trypsin and chymotrypsin. I dephosphorylated myosin light chains but was not active toward intact myosin or heavy meromyosin. However, when Ic was dissocd. from both regulatory subunits or from the 55,000-Da polypeptide, I became active toward myosin, suggesting that the 55,000-Da polypeptide inhibits the activity of the Ic toward myosin. In addn. to alteration of the substrate specificity, the regulatory subunits also modulated the effect of divalent cations like Mn2+ on the activity of the enzyme.
IT **9025-75-6**
RL: BIOL (Biological study)
(I, of smooth muscle, substrate specificity of, limited proteolysis and dissocn. effect on)

L117 ANSWER 113 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:591996 HCAPLUS

DN 103:191996
TI Purification and characterization of a smooth muscle myosin phosphatase from turkey gizzards
AU Pato, Mary D.; Kerc, Ewa
CS Dep. Biochem., Univ. Saskatchewan, Saskatoon, SK, S7N 0W0, Can.
SO J. Biol. Chem. (**1985**), 260(22), 12359-66
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB A **phosphoprotein phosphatase** that dephosphorylates smooth muscle myosin was purified to apparent homogeneity from turkey gizzards. Smooth muscle phosphatase (SMP) IV has a mol. wt. (Mr) of 150,000, as detd. by gel filtration on a Sephadex G-200 column, and is composed of 2 subunits (Mr = 58,000 and 40,000). Although the phosphatase is active toward a no. of proteins, its activities toward the contractile proteins (intact myosin, heavy meromyosin, and isolated myosin light chains) are higher than its activities toward phosphorylase a, histone IIA, and phosphorylase kinase. SMP-IV preferentially dephosphorylates the .beta.-subunit of phosphorylase kinase. The properties of the enzyme were studied with heavy meromyosin (a sol. chymotryptic fragment of myosin) and isolated myosin light chains as substrates. SMP-IV has high affinity for both substrates and is optimally active at neutral pH. The divalent cations Ca2+ and Mg2+ activate the dephosphorylation of heavy meromyosin but inhibit the activity toward myosin light chains. Low concns. of ATP (1-5 mM) activate SMP-IV, but concns. >5 mM are inhibitory. The enzyme is inhibited 50% by NaF and pyrophosphate concns. of >10 mM. Rabbit skeletal muscle heat-stable inhibitor-2 has no effect on the activity of SMP-IV toward heavy meromyosin, myosin light chains, or phosphorylase a.

L117 ANSWER 114 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:576755 HCAPLUS
DN 103:176755
TI Immunological characterization of **phosphoprotein phosphatases**
AU Shacter, Emily; McClure, Joseph A.; Korn, Edward D.; Chock, P. Boon
CS Lab. Biochem., Natl. Heart, Lung, Blood Inst., Bethesda, MD, 20892, USA
SO Arch. Biochem. Biophys. (**1985**), 242(2), 523-31
CODEN: ABBIA4; ISSN: 0003-9861
DT Journal
LA English
AB **Phosphoprotein phosphatases** regulate the biol. activities of proteins through their involvement in cyclic phosphorylation/dephosphorylation cascades. A variety of multimeric phosphatases have been isolated and grouped into several classes, termed type 1 and types 2A, 2B, and 2C. To elucidate the relationship between the different **phosphoprotein phosphatases**, highly purified enzymes from soil amebae, turkey gizzards, bovine heart and brain, and rabbit skeletal muscle and reticulocytes were tested for immunol. antigenic relatedness. Two heterologous antibody prepns. were employed for this purpose. One was made against an Acanthamoeba type 2A phosphatase and the other was made to bovine brain phosphatase type 2B (**calcineurin**, holoenzyme). Specific subunity cross-reactivity was examd. by protein blot (Western) anal. The antibody to the type 2A phosphatase reacted with the catalytic subunits of every type 2 enzyme tested, including both the catalytic and Ca2+-binding subunits of the Ca2+/calmodulin-dependent type 2B phosphatase (**calcineurin**), bovine cardiac type 2A phosphatase, and turkey gizzard smooth muscle phosphatase-1 (type 2A1). It did not react with any type 1 phosphatase (catalytic subunity or ATP-Mg-dependent). The antigenic relatedness of **calcineurin** and the bovine cardiac type 2A phosphatase (mol. wt. 38,000) was demonstrated further by protein blot anal. showing that the anti-**calcineurin** antibody cross-reacted with both enzymes. The mutual cross-reactivity poses an intriguing problem because these enzymes are so different in their **mol. structures** and modes of regulation. The degree of evolutionary conservation exhibited by the antigenic cross-reactivity of the type 2 enzymes from a broad range of

species and tissues suggests a strong selective pressure on maintaining one or more features of these important regulatory enzymes.

IT **9025-75-6**
RL: BIOL (Biological study)
(antigenic cross-reactivity of)

L117 ANSWER 115 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:500687 HCAPLUS
DN 103:100687
TI **Calcineurin**, a calmodulin-stimulated protein phosphatase
AU Manalan, Allan S.; Klee, Claude B.
CS Lab. Biochem., Natl. Cancer Inst., Bethesda, MD, 20205, USA
SO Calcium Biol. Syst., [Proc. Annu. Meet. Fed. Am. Soc. Environ. Biol.], 67th (**1985**), Meeting Date 1983, 307-15. Editor(s): Rubin, Ronald P.; Weiss, George B.; Putney, James W., Jr. Publisher: Plenum, New York, N. Y.
CODEN: 54BSAG
DT Conference; General Review
LA English
AB A review, with 38 refs., of the relation between the subunit structure and phosphatase activity of **calcineurin**.
IT **9025-75-6**
RL: BIOL (Biological study)
(calmodulin-stimulated, of **calcineurin**, subunit structure in relation to)

L117 ANSWER 116 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:484214 HCAPLUS
DN 103:84214
TI Effect of ionizing radiation on rat liver **phosphoprotein phosphatase**
AU Vinogradova, R. P.; Kucherenko, N. E.; Demchenko, I. B.
CS Biol. Fac., T. G. Shevchenko Kiev State Univ., Kiev, USSR
SO Radiobiologiya (**1985**), 25(3), 399-402
CODEN: RADOA8; ISSN: 0033-8192
DT Journal
LA Russian
AB **Phosphoprotein phosphatase** (EC 3.1.3.16) (I) with high specificity for lysyl-tRNA synthetase and proteins of the high-mol.-wt. aminoacyl-tRNA synthetase complex was isolated from the livers of rats exposed to a LD (of 0.21 C/kg) of x-irradn. Irradn. decreased I 3-4-fold at 1 h after treatment. At 24 h after irradn., I activity had increased but did not reach control levels. Lysyl-tRNA synthetase and proteins of the multienzyme synthetase complexes from irradiated livers were less effective substrates than proteins from control livers.
IT **9025-75-6**
RL: BIOL (Biological study)
(of liver, of irradiated mammal)

L117 ANSWER 117 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:483998 HCAPLUS
DN 103:83998
TI **Phosphoprotein phosphatase** from bovine spleen cell nuclei: physicochemical properties
AU Rezyapkin, V. I.; Leonova, L. E.; Komkova, A. I.
CS Fac. Biol., A. A. Zhdanov Leningrad State Univ., Leningrad, USSR
SO Biokhimiya (Moscow) (**1985**), 50(7), 1067-75
CODEN: BIOHAO; ISSN: 0006-307X
DT Journal
LA English
AB The physicochem. properties of **phosphoprotein phosphatase** (EC 1.3.1.16) from bovine spleen cell nuclei were investigated. The enzyme possesses a wide substrate specificity and catalyzes dephosphorylation of phosphocasein, ATP, ADP, and p-nitrophenylphosphate (pNPP) with Km values of 0.44, 0.43, and 1.25 mM, resp. The mol. wt. of the enzyme, as detd. by gel filtration on Sephadex

G-75 and electrophoresis in polyacrylamide gel of different concns., is .apprx.33,000. SDS-polyacrylamide gel electrophoresis revealed 2 protein bands with mol. wts. of 12,000 and 18,000. The enzyme mol. predominantly contains acidic amino acid residues, 2 free SH groups, and 2 SS bonds. **Phosphoprotein phosphatase** is a glycoprotein with a carbohydrate content of .apprx.22%, and has an addnl. absorption max. at 560 nm. The enzyme is competitively inhibited by NH4 molybdate (Ki = 0.37 .mu.M) and noncompetitively by NaF (Ki = 1.3 mM). Incubation of **phosphoprotein phosphatase** with 2 mM PMSF for 25 h resulted in an .apprx.46% loss of activity. NH4 molybdate, NaF, and PMSF reversibly inhibit the enzyme. Modification of amino acid SH and NH2 groups and histidine leads to decreased activity. Incubation of **phosphoprotein phosphatase** with [.gamma.-33P]ATP resulted in the incorporation of 0.33 mol of 33P/mol of enzyme. The mechanism of the enzyme-catalyzed hydrolysis of the phosphoester bond is discussed.

IT **9025-75-6**
RL: BIOL (Biological study)
(of spleen nucleus, physicochem. properties of)

L117 ANSWER 118 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:200096 HCAPLUS
DN 102:200096
TI The protein phosphatases involved in cellular regulation. 2. Purification, subunit structure and properties of protein phosphatases-2A0, 2A1, and 2A2 from rabbit skeletal muscle
AU Tung, H. Y. Lim; Alemany, Susana; Cohen, Philip
CS Dep. Biochem., Univ. Dundee, Dundee, UK
SO Eur. J. Biochem. (**1985**), 148(2), 253-63
CODEN: EJBCAI; ISSN: 0014-2956
DT Journal
LA English
AB **Phosphoprotein phosphatases**-2A0, 2A1, and 2A2 were purified to homogeneity from rabbit skeletal muscle. Approx. 1 mg of phosphatase-2A0 and 2A1, and 0.5 mg of phosphatase-2A2, was isolated from 4000 g muscle within 10 days. **Phosphoprotein phosphatases**-2A0 and 2A1 each comprised 3 subunits, termed A, B', and C (2A0) or A, B, and C (2A1), whereas phosphatase-2A2 contained only 2 subunits, A and C. The A and C components of phosphatases-2A0, 2A1, and 2A2 had indistinguishable mobilities on SDS-polyacrylamide gels and identical peptide maps. By these criteria, the C component was also identical to the catalytic subunit of phosphatase-2A purified from EtOH-treated muscle exts. The electrophoretic mobilities of the B and B' subunits were slightly different, and their peptide maps were distinct. The mol. wts. of the native enzymes detd. by sedimentation equil. centrifugation were 181 kilodaltons (kDa) (2A0), 202 kDa (2A1), and 107 kDa (2A2), whereas those of the subunits estd. by SDS-polyacrylamide gel electrophoresis were 60 kDa (A), 55 kDa (B), 54 kDa (B'), and 36 kDa (C). These values, in conjunction with molar ratios estd. by densitometric analyses of the gels, suggested that the subunit structures of the enzymes were AB'C2 (2A0), ABC2 (2A1), and AC (2A2). **Phosphoprotein phosphatase**-2A2 appeared to be derived from 2A0 and(or) 2A1 during purifn. through degrdn. or dissocn. of the B' and(or) B subunits. **Phosphoprotein phosphatases**-2A0, 2A1, and 2A2 were the only phosphorylase phosphatases in rabbit skeletal muscle that were activated by the basic proteins, protamine, histone H1, and polylysine. Activation by protamine varied over 5-20-fold for phosphatase-2A0 and 5-7-fold for phosphatases-2A1 and 2A2. The dephosphorylation of glycogen synthase was activated by basic proteins in a similar manner to the phosphorylase phosphatase activity. The isolated C subunit was also stimulated by histone H1 and protamine, but 5-10-fold higher concns. were required, and with phosphorylase as substrate, max. activation was only .apprx.2-fold. Activation by basic proteins appeared to involve their interaction with the A and(or) C subunits, but not with the B or B' subunits, or the substrates, phosphorylase and glycogen synthase.

IT **9025-75-6P**

RL: PREP (Preparation)
(2A, multiple forms of, of muscle, purifn. and properties and subunit structure of)

L117 ANSWER 119 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:181248 HCAPLUS
DN 102:181248
TI On the 6-phosphofructo-1-kinase phosphatase activity of protein phosphatase 2C and its dimeric nature
AU Mieskes, Gottfried; Soeling, Hans Dieter
CS Zent. Innere Med., Univ. Goettingen, Goettingen, 3400, Fed. Rep. Ger.
SO FEBS Lett. (**1985**), 181(1), 7-11
CODEN: FEBLAL; ISSN: 0014-5793
DT Journal
LA English
AB Chromatog. on histone-Sepharose, gel filtration expts. on Sephacryl S-200 and Sephadex G-100, as well as sucrose d. gradient centrifugation show that 6-phosphofructo-1-kinase phosphatase (PFK-phosphatase) and **phosphoprotein phosphatase** 2C prepns. behave identically under all exptl. conditions used. The low activity of PFK-phosphatase phosphorylated histone H2B which had been previously reported had resulted from an inhibition of the enzyme by high concns. of this substrate. The apparent mol. wt. of **phosphoprotein phosphatase** 2C as calcd. from Sephacryl chromatog. and sedimentation anal. was .apprx.90 kilodaltons (kDa); the mol. wt. obtained by SDS-gel electrophoresis was .apprx.45 kDa. The native enzyme therefore appeared to be a dimer consisting probably of 2 identical subunits. Accordingly, the previously described PFK-phosphatase is **phosphoprotein phosphatase** 2C.
IT **9025-75-6**
RL: BIOL (Biological study)
(2C, of liver, phosphofructokinase phosphatase identity with)

L117 ANSWER 120 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1985:127817 HCAPLUS
DN 102:127817
TI Adenosine 5'-diphosphate as an allosteric effector of phosphorylase kinase from rabbit skeletal muscle
AU Cheng, Alexander; Fitzgerald, Thomas J.; Carlson, Gerald M.
CS Med. Cent., Univ. Mississippi, Jackson, MS, 39216-4505, USA
SO J. Biol. Chem. (**1985**), 260(4), 2535-42
CODEN: JBCHA3; ISSN: 0021-9258
DT Journal
LA English
AB Equil. binding and activity studies indicate that ADP binds to phosphorylase kinase with high affinity at a site, or sites, distinct from the catalytic site. Equil. dialysis at pH 6.8 and 8.2, with and without Mg2+, and with phosphorylated and nonphosphorylated enzyme prepns. revealed .apprx.8 ADP binding sites per .alpha.4.beta.4.gamma.4.delta.4 hexadecamer, with Kd (dissocn. const.) values of 0.26-17 .mu.M. Decreasing the pH from 8.2 to 6.8 or removing the Mg2+ enhanced the affinity for ADP. At pH 6.8, ADP stimulated the phosphorylase conversion and autophosphorylation activities of the nonactivated enzyme. Analogs of ADP with modifications at the 2'-, 3'-, and 5'-positions allowed detn. of structural requirements for the stimulation of activity. ADP seems to alter the conformation of the .beta. subunit, as addn. of the nucleotide inhibits its dephosphorylation by **phosphoprotein phosphatase** and its chem. crosslinking by 1,5-difluoro-2,4-dinitrobenzene. The binding affinities and effects of ADP suggest that it may function physiol. as an allosteric effector of phosphorylase kinase.
IT **9025-75-6**
RL: BIOL (Biological study)
(phosphorylase kinase dephosphorylation by, ADP inhibition of)

L117 ANSWER 121 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:586731 HCAPLUS

DN 101:186731
TI Properties of a **phosphoprotein phosphatase** from skeletal muscle and its regulation in diabetes
AU Khatra, Balwant S.
CS Med. Sch., Vanderbilt Univ., Nashville, TN, 37232, USA
SO Proc. Soc. Exp. Biol. Med. (**1984**), 177(1), 33-41
CODEN: PSEBAA; ISSN: 0037-9727
DT Journal
LA English
AB **Phosphoprotein phosphatase** was isolated from glycogen-protein complexes of rabbit skeletal muscle and its physicochem. properties were ascertained. In addn., the catalytic properties of glycogen synthase D and its phosphatases from muscle of normal and diabetic animals were compared. The phoshoprotein phosphatase had a mol. wt. of 83 kilodaltons (K); catalytic activity resided in a subunit of 38K. An assocd. 75K protein was inactive; its function and the specificity of its assocn. with the enzyme are uncertain. Comparison of the dephosphorylation of glycogen synthase D from normal and diabetic animals by phosphatases from both sources indicated that the glycogen synthase phosphatase activity of the **phosphoprotein phosphatase** prepn. was inhibited in diabetes and that synthase D from diabetic rabbits was dephosphorylated only 50% as efficiently as the enzyme from normal animals by the phosphatase from either muscle prepn. A brief review and discussion of other properties of **phosphoprotein phosphatases** is also presented.
IT **9025-75-6P**
RL: PREP (Preparation)
(of skeletal muscle, purifn. and characterization of)

L117 ANSWER 122 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1982:419475 HCAPLUS
DN 97:19475
TI Regulation of protein phosphatase 1 via glycogen phosphorylase
AU Madsen, Neil B.; Fletterick, R. J.; Kasvinsky, Peter J.
CS Dep. Biochem., Univ. Alberta, Edmonton, AB, T6G 2H7, Can.
SO Cold Spring Harbor Conf. Cell Proliferation (**1981**), 8(Protein Phosphorylation, Book A), 483-95
CODEN: CSHCAL; ISSN: 0097-5230
DT Journal; General Review
LA English
AB A review and discussion with 24 refs. on the inhibition of protein phosphatase by glycogen phosphorylase and on the **mol. structure** of the phosphorylase.
IT **9025-75-6**
RL: PROC (Process)
(inhibition of, by phosphorylase a)

L117 ANSWER 123 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1981:187810 HCAPLUS
DN 94:187810
TI Effect of whole-body **x-ray** irradiation on the activity of some enzymes of carbohydrate-phosphorus metabolism in chicken tissues
AU Parsadanyan, H. K.; Simonyan, A. A.; Ter-Tatevosyan, L. P.
CS Inst. Biokhim., Yerevan, USSR
SO Zh. Eksp. Klin. Med. (**1980**), 20(6), 588-94
CODEN: ZKMAAX; ISSN: 0514-7484
DT Journal
LA Russian
AB Exposure of chickens to whole-body x-irradn. (800 R) decreased ATPase (EC 3.6.1.3) and increased glycogen phosphorylase (EC 2.4.1.1) activities in the heart and liver 3-7 days after exposure. **Phosphoprotein phosphatase** (EC 3.1.3.16) decreased in liver and heart submitochondrial supernatant and in liver mitochondria at 3 days after exposure and increased above normal at 7 days after exposure. In liver mitochondria and heart submitochondrial supernatant, the enzyme activity decreased after the 7th day of exposure, but remained elevated in the

liver submitochondrial supernatant.
IT **9025-75-6**
RL: BIOL (Biological study)
(of heart and liver, of chicken, **x-ray** effect on)

L117 ANSWER 124 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1979:536173 HCAPLUS
DN 91:136173
TI **Computer** simulation of metabolism in pyruvate-perfused rat heart. III. Pyruvate dehydrogenase
AU Kohn, Michael C.; Achs, Murray J.; Garfinkel, David
CS Moore Sch. Electr. Eng., Univ. Pennsylvania, Philadelphia, PA, 19104, USA
SO Am. J. Physiol. (**1979**), 237(3), R167-R173
CODEN: AJPHAP; ISSN: 0002-9513
DT Journal
LA English
AB A physiol. and biochem. realistic model of the regulation of pyruvate dehydrogenase complex (PDH) was constructed for the perfused rat heart. It includes conversion between inactive (phospho) and active (dephospho) forms by a specific protein kinase (PDHK) and **phosphoprotein phosphatase** (PDHP). The activity of the tightly bound PDHK is influenced by synergistic activation/inhibition by acetyl-CoA/CoASH and NADH/NAD. PDHK in this simulation was more sensitive to the fraction of ADP that was Mg2+-chelated than to the ATP/ADP ratio. Ca2+ stimulates binding of Mg2+-dependent PDHP to the complex; the bound enzyme was considered to be the active species. The fraction of PDH in the active form, rather than substrate and inhibitor levels, dets. PDH activity under these conditions. This fraction depends on the present value and recent history of the difference between PDHK and PDHP activities. Both of these are active continuously and continuously control PDH.

L117 ANSWER 125 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1976:442901 HCAPLUS
DN 85:42901
TI A kinetic analysis of the dephosphorylation, by bovine spleen **phosphoprotein phosphatase** (EC 3.1.3.16) of a phosphopeptide derived from .beta.-casein
AU West, David W.; Dalgleish, Douglas G.
CS Hannah Res. Inst., Univ. Glasgow, Glasgow, Scot.
SO Biochim. Biophys. Acta (**1976**), 438(1), 169-75
CODEN: BBACAQ
DT Journal
LA English
AB A peptide contg. the 4 closely grouped phosphoseryl residues present in .beta.-casein was enzymically dephosphorylated with bovine spleen **phosphoprotein phosphatase**. The course of dephosphorylation reaction was followed by cellulose acetate electrophoresis and the amt. of partially phosphorylated peptides present at each stage quantified by the same method. The phosphate groups are removed in a sequential manner. The rate consts. for each stage of the dephosphorylation were **computed** from the data obtained. The rate consts. indicate that interaction in the intact peptide results in an enhancement of the activity of the phosphoseryl cluster.
IT **9025-75-6**
RL: RCT (Reactant)
(.beta.-casein phosphopeptide hydrolysis by, kinetics of)

L117 ANSWER 126 OF 126 HCAPLUS COPYRIGHT 2000 ACS
AN 1976:146789 HCAPLUS
DN 84:146789
TI The effect of several diphosphonates on acid phosphohydrolases and other lysosomal enzymes
AU Felix, Rolf; Russell, R. Graham G.; Fleisch, Herbert
CS Dep. Pathophysiol., Univ. Berne, Berne, Switz.
SO Biochim. Biophys. Acta (**1976**), 429(2), 429-38
CODEN: BBACAQ

DT Journal
LA English
AB Diphosphonates are known to inhibit bone resorption in tissue culture and in exptl. animals. This effect may be due to their ability to inhibit the dissoln. of hydroxyapatite **crystals**, but other mechanisms may be important. Since lysosomal enzymes have been implicated in the process of bone resorption, the effect was examd. of several phosphonates and of a polyphosphate (P20,i) on lysosomal hydrolases derived from rat liver and rat bone. Dichloromethylene diphosphonate (I) strongly inhibited acid .beta.-glycerophosphatase and acid p-nitrophenyl phosphatase (II) and to a lesser degree (in descending order) acid pyrophosphatase, arylsulfatase A, DNase II, and **phosphoprotein phosphatase** of rat liver. Inhibition of II and arylsulfatase A was competitive. Ethane-1-hydroxy-1,1-diphosphonate (III) did not inhibit any of these enzymes, except at high concns. Neither I nor III had any effect on .beta.-glucuronidase, arylesterase, and cathepsin D. Of several other phosphonates tested, only undec-10-ene-1-hydroxy-1,1-diphosphonic acid inhibited II strongly; P20,i had little effect. II in rat calvaria ext. behaved in the same way as the liver enzyme and was also strongly inhibited by I, but not by III. It is suggested that the inhibition of bone resorption by I might be due in part to a direct effect of this diphosphonate on lysosomal hydrolases.

=> d all 11

L126 ANSWER 11 OF 11 HCAPLUS COPYRIGHT 2000 ACS
AN 1984:402511 HCAPLUS
DN 101:2511
TI The **structure** of **calcineurin** B
AU Aitken, Alastair; Klee, Claude B.; Stewart, Alexander A.; Tonks, Nicholas K.; Cohen, Philip
CS Dep. Biochem., Univ. Dundee, Dundee, UK
SO Dev. Biochem. (**1983**), 25(Calcium-Binding Proteins), 113-19
CODEN: DEBIDR; ISSN: 0165-1714
DT Journal
LA English
CC 6-3 (General Biochemistry)
Section cross-reference(s): 7
AB The complete amino acid sequence of bovine brain **calcineurin** subunit B is reported. **Calcineurin** B has overall sequence homol. with calmodulin, and the N-terminal sequence, which is blocked by myristic acid, is homologous to the corresponding N-terminal blocked sequences of the catalytic subunit of cAMP-dependent protein kinase and the p15 protein of murine leukemia virus. The Ca2+-binding sites were assigned by homol. with those of parvalbumin. The predicted conformation is 54% .alpha.-helical and 13% .beta.-pleated sheet.
ST **calcineurin** B sequence brain
IT Brain, composition
(**calcineurin** B subunit of, amino acid sequence of)
IT **Conformation** and **Conformers**
(of **calcineurin** B subunit, of bovine brain)
IT Protein sequences
(of **calcineurin** B subunit, of bovine brain, complete)
IT Proteins
RL: BIOL (Biological study)
(**calcineurins**, amino acid sequence of B subunit of, of bovine brain)
IT **90371-51-0**
RL: PRP (Properties)
(amino acid sequence of)

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L127 5567 S L6 OR PHOSPHOPROTEIN PHOSPHATASE
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L130 3 S L127 AND 32300/CC
L131 52 S L127 AND ?CRYS?
L132 22 S L127 AND (3D OR THREE DIMENSION?)
L133 1167 S L127 AND STRUCTURE
L134 6 S L128-L130 AND L131-L133
L135 50 S L128-L130 NOT L134
L136 51 S L131 NOT L134,L135
L137 14 S L136 AND (CRYSTAL STRUCTURE OR THREE? OR CRYSTALLIZATION)/TI
L138 3173 S L127 AND PY<=1995
L139 10 S L138 AND (ARMISTEAD D? OR FITZGIBBON ? OR FLEMING M? OR GRIFF
L140 24 S L137,L139
L141 208 S L133 AND L138
L142 28 S L141 AND 00520/CC
L143 23 S L141 AND CONFERENCE/DT
L144 26 S L142 AND (CONGRESS OR CONFERENCE OR POSTER OR SYMPOS? OR MEET
L145 52 S L140,L142-L144
L146 21 S L131 AND L138
L147 61 S L145,L146
L148 16 S L138 AND THREE DIMENSION?
L149 71 S L147,L148
L150 65 S L138 AND L149

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L150 ANSWER 1 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1996:59000 BIOSIS
DN PREV199698631135
TI **Crystal structure** of the catalytic subunit of human protein phosphatase 1 and its complex with tungstate.
AU Egloff, Marie-Pierre; Cohen, Patricia T. W.; Reinemer, Peter; Barford, David (1)
CS (1) Lab. Molecular Biophysics, Univ. Oxford, The Rex Richards Build., South Parks Road, Oxford OX1 3QU UK
SO Journal of Molecular Biology, (1995) Vol. 254, No. 5, pp. 942-959. ISSN: 0022-2836.
DT Article
LA English
AB Protein phosphatase 1 (PP1) is a serine/threonine protein phosphatase that is essential in regulating diverse cellular processes. Here we report the **crystal** structure of the catalytic subunit of human PP1-gamma-1 and its complex with tungstate at 2.5 ANG resolution. The anomalous scattering from tungstate was used in a multiple wavelength anomalous

dispersion experiment to derive **crystallographic** phase information. The protein adopts a single domain with a novel fold, distinct from that of the protein tyrosine phosphatases. A di-nuclear ion centre consisting of Mn-2+ and Fe-2+ is situated at the catalytic site that binds the phosphate moiety of the substrate. Proton-induced X-ray emission spectroscopy was used to identify the nature of the ions bound to the enzyme. The structural data indicate that dephosphorylation is catalysed in a single step by a metal-activated water molecule. This contrasts with other phosphatases, including protein tyrosine phosphatases, acid and alkaline phosphatases which form phosphoryl-enzyme intermediates. The structure of PP1 provides insight into the molecular mechanism for substrate recognition, enzyme regulation and inhibition of this enzyme by toxins and tumour promoters and a basis for understanding the expanding family of related phosphatases which include PP2A and PP2B (**calcineurin**).

CC Cytology and Cytochemistry - Human *02508
Comparative Biochemistry, General *10010
Biochemical Methods - General *10050
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Methods - Minerals *10059
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals *10069
Biophysics - General Biophysical Studies *10502
Biophysics - General Biophysical Techniques *10504
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - General and Comparative Studies; Coenzymes *10802
Enzymes - Methods *10804
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Physiology, General and Miscellaneous - General *12002
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Minerals *13010
Metabolism - Proteins, Peptides and Amino Acids *13012
Toxicology - General; Methods and Experimental *22501

BC Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Methods and Techniques; Physiology; Toxicology

IT Chemicals & Biochemicals
PROTEIN PHOSPHATASE; TUNGSTATE

IT Miscellaneous Descriptors
ANALYTICAL METHOD; CATALYTIC SUBUNIT; CELLULAR PROCESSES; **CRYSTALLOGRAPHIC** PHASE INFORMATION; **CRYSTALLOGRAPHY**; ENZYME COMPARISONS; ENZYME INHIBITORS; HUMAN ENZYMES; MOLECULAR BIOLOGY; MOLECULAR STRUCTURE; PROTON-INDUCED X-RAY EMISSION SPECTROSCOPY; REGULATION

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN **9025-75-6** (PROTEIN PHOSPHATASE)
12737-86-9 (TUNGSTATE)

L150 ANSWER 2 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1996:55383 BIOSIS
DN PREV199698627518
TI **Crystal structures** of human **calcineurin** and the human FKBP12-FK506-**calcineurin** complex.
AU Kissinger, Charles R.; Parge, Hans E.; Knighton, Daniel R.; Lewis, Cristina T.; Pelletier, Laura A.; Tempczyk, Anna; Kalish, Vincent J.; Tucker, Kathleen D.; Showalter, Richard E.; Moomaw, Ellen W.; Gastinel, Louis N.; Habuka, Noriyuki; Chen, Xinghai; Maldonado, Fausto; Barker, John

E.; Bacquet, Russell; Villafranca, J. Ernest (1)
CS (1) Agouron Pharm. Inc., 3565 General Atomics Court, San Diego, CA 92121-1121 USA
SO Nature (London), (1995) Vol. 378, No. 6557, pp. 641-644. ISSN: 0028-0836.
DT Article
LA English
AB **Calcineurin** (CaN) is a calcium- and calmodulin-dependent protein serine/threonine phosphatase which is critical for several important cellular processes, including T-cell activation. CaN is the target of the immunosuppressive drugs cyctosporin A and FK506, which inhibit CaN after forming complexes with cytoplasmic binding proteins (cyclophilin and FKBP12, respectively). We report here the **crystal** structures of full-length human CaN at 2.1 ANG resolution and of the complex of human CaN with FKBP12-FK506 at 3.5 ANG resolution. In the native CaN structure, an autoinhibitory element binds at the Zn/Fe-containing active site. The metal-site geometry and active-site water structure suggest a catalytic mechanism involving nucleophilic attack on the substrate phosphate by a metal-activated water molecule. In the FKBP12-FK506-CaN complex, the auto-inhibitory element is displaced from the active site. The site of binding of FKBP12-FK506 appears to be shared by other non-competitive inhibitors of **calcineurin**, including a natural anchoring protein.
CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
CALCINEURIN
IT Miscellaneous Descriptors
NON-COMPETITIVE INHIBITION
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN **9025-75-6 (CALCINEURIN)**

L150 ANSWER 3 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1996:37172 BIOSIS
DN PREV199698609307
TI Effect of orthovanadate on commitment of avian myoblasts transformed with Rous sarcoma virus to myogenic differentiation.
AU Hase, Hidenori; Isobe, Akiko; **Kim, Jeman (1)**
CS (1) Inst. Molecular Cellular Biol. Pharmaceutical Sci., Kyoto Pharmaceutical Univ., Yamashina-ku, Kyoto 607 Japan
SO European Journal of Cell Biology, (1995) Vol. 68, No. 3, pp. 313-322. ISSN: 0171-9335.
DT Article
LA English
AB Myogenic differentiation of quail myoblasts transformed with a temperature-sensitive mutant of Rous sarcoma virus (QM-RSV cells) depends on the temperature: at 35.5 degree C, the permissive temperature for the virus, the transformed myoblasts proliferate, without fusion. but at 41 degree C, the nonpermissive temperature, they become committed to myogenic differentiation until about 10 h and then myoblast fusion occurs within 24 h. This temperature dependency of the differentiation reaction is derived from protein kinase activity of src gene product. Thus, at 41 degree C, the differentiation proceeds with dephosphorylation of the proteins. For further clarification of relationship between the protein phosphorylation and the control of differentiation, the events during differentiation were

examined using inhibitors of tyrosine kinase and phosphatase, respectively. To examine the role of phosphotyrosyl protein phosphatases in skeletal muscle differentiation, these cells were treated with sodium orthovanadate, a potent inhibitor of the enzyme. The treatment with the drug inhibited myoblast fusion and creatine kinase activity of the cells at 41 degree C, with inhibition of tyrosine dephosphorylation. Moreover, the treatment of the cells with vanadate for 12 h at 41 degree C, followed by the removal of the drug resulted in myoblast fusion after the lag time about 12 h. On the other hand, herbimycin A was needed to acquire the fusion commitment at 35.5 degree C. These results are suggestive evidence to reflect that tyrosine dephosphorylation is a key step in commitment of QM-RSV cells to myogenic differentiation. Examination of the tyrosine phosphorylated proteins indicated that vanadate mainly inhibited the dephosphorylations of 70-, 58-, and 36-kDa proteins, suggesting that these proteins may be closely associated with the steps involved in commitment to myogenic differentiation.

CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Chemical and Physical *10806
Muscle - Physiology and Biochemistry *17504
Developmental Biology - Embryology - Morphogenesis, General *25508
Genetics of Bacteria and Viruses *31500
Virology - Animal Host Viruses *33506

BC Retroviridae 02623
Galliformes *85536

IT Major Concepts
Cell Biology; Development; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Microbiology; Muscular System (Movement and Support)

IT Chemicals & Biochemicals
ORTHOVANADATE; PROTEIN PHOSPHATASE; PROTEIN KINASE

IT Miscellaneous Descriptors
CREATINE KINASE; PHOSPHORYLATION; PROTEIN KINASE; PROTEIN PHOSPHATASE; SRC GENE PRODUCT

ORGN Super Taxa
Galliformes: Aves, Vertebrata, Chordata, Animalia; Retroviridae: Viruses

ORGN Organism Name
quail (Galliformes); Retroviridae (Retroviridae)

ORGN Organism Superterms
animals; birds; chordates; microorganisms; nonhuman vertebrates; vertebrates; viruses

RN 14333-18-7 (ORTHOVANADATE)
9025-75-6 (PROTEIN PHOSPHATASE)
9026-43-1 (PROTEIN KINASE)

L150 ANSWER 4 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1996:26555 BIOSIS
DN PREV199698598690
TI Structure comparison of native and mutant human recombinant FKBP12 complexes with the immunosuppressant drug FK506 (tacrolimus.
AU Itoh, Susumu (1); Navia, Manuel A.
CS (1) Vertex Pharm. Inc., 40 Allison St., Cambridge, MA 02139-4211 USA
SO Protein Science, (1995) Vol. 4, No. 11, pp. 2261-2268.
ISSN: 0961-8368.
DT Article
LA English
AB The consequences of site-directed mutagenesis experiments are often anticipated by empirical rules regarding the expected effects of a given amino acid substitution. Here, we examine the effects of "conservative" and "nonconservative" substitutions on the X-ray **crystal** structures of human recombinant FKBP 12 mutants in complex with the immunosuppressant drug FK506 (tacrolimus). R42K and R421 mutant complexes show 110-fold and 180-fold decreased **calcineurin** (CN)

inhibition, respectively, versus the native complex, yet retain full peptidyl prolyl isomerase (PPIase) activity, FK506 binding, and FK506-mediated PPIase inhibition. Interestingly, the structure of the R421 mutant complex is better conserved than that of the R42K mutant complex when compared to the native complex structure, within both the FKBP 12 protein and FK506 ligand regions of the complexes, and with respect to temperature factors and RMS coordinate differences. This is due to compensatory interactions mediated by two newly ordered water molecules in the R421 complex structure, molecules that act as surrogates for the missing arginine guanidino nitrogens of R42. The absence of such surrogate solvent interactions in the R42K complex leads to some disorder in the so-called "40s loop" that encompasses the substituent. One rationalization proposed for the observed loss in CN inhibition in these R42 mutant complexes invokes indirect effects leading to a misorientation of FKBP12 and FK506 structural elements that normally interact with **calcineurin**. Our results with the structure of the R421 complex in particular suggest that the observed loss of CN inhibition might also be explained by the loss of a specific R42-mediated interaction with CN that cannot be mimicked effectively by the solvent molecules that otherwise stabilize the conformation of the 40s loop in that structure.

CC Genetics and Cytogenetics - Human *03508
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Clinical Immunology (Human Medicine, Medical Sciences); Genetics; Pharmacology

IT Chemicals & Biochemicals
FK506; TACROLIMUS; **CALCINEURIN**

IT Miscellaneous Descriptors
AMINO ACID SUBSTITUTION; **CALCINEURIN** INHIBITION; FK506; IMMUNOPHILINS; IMMUNOSUPPRESSANT-DRUG; SITE-DIRECTED MUTAGENESIS; STRUCTURE-BASED DRUG DESIGN; TACROLIMUS; X-RAY **CRYSTALLOGRAPHY**

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 104987-11-3 (FK506)
104987-11-3 (TACROLIMUS)
9025-75-6 (**CALCINEURIN**)

L150 ANSWER 5 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1995:553831 BIOSIS

DN PREV199698568131

TI Insights derived from the structures of the Ser/Thr phosphatases **calcineurin** and protein phosphatase 1.

AU Lohse, D. L.; Denu, J. M.; Dixon, J. E.

CS Dep. Biol. Chemistry, Univ. Michigan Medical School, Ann Arbor, MI 48109-0606 USA

SO Structure (London), (1995) Vol. 3, No. 10, pp. 987-990.
ISSN: 0969-2126.

DT General Review

LA English

CC Comparative Biochemistry, General *10010
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals *10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Pharmacology - General *22002

Pharmacology - Immunological Processes and Allergy *22018
Physiology and Biochemistry of Bacteria *31000
Plant Physiology, Biochemistry and Biophysics - Enzymes *51518
Invertebrata, Comparative and Experimental Morphology, Physiology and Pathology - Insecta - Physiology *64076

BC Myoviridae 02707
Siphoviridae 02710
Enterobacteriaceae 06702
Endospore-forming Gram-Positives 07810
Ascomycetes 15100
Leguminosae 26260
Diptera 75314
Leporidae 86040
Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Pharmacology; Physiology

IT Chemicals & Biochemicals
PROTEIN PHOSPHATASE; FK506; CYCLOSPORIN; SERINE; MICROCYSTIN

IT Sequence Data
molecular sequence data

IT Miscellaneous Descriptors
BACTERIOPHAGE-LAMBDA; CYCLOSPORIN; ENZYME INHIBITOR AGENT DESIGN; FK506; IMMUNOSUPPRESSANT AGENT; INTERSPECIFIC AMINO ACID SEQUENCE COMPARISON; METALLO-PHOSPHOESTERASE MOTIF; MICROCYSTIN; MOLECULAR MODEL; SERINE/THREONINE PHOSPHATASE; **THREE-DIMENSIONAL** STRUCTURE

ORGN Super Taxa
Ascomycetes: Fungi, Plantae; Chroococcales: Cyanobacteria, Eubacteria, Bacteria; Diptera: Insecta, Arthropoda, Invertebrata, Animalia; Endospore-forming Gram-Positives: Eubacteria, Bacteria; Enterobacteriaceae: Eubacteria, Bacteria; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Leguminosae: Dicotyledones, Angiospermae, Spermatophyta, Plantae; Leporidae: Lagomorpha, Mammalia, Vertebrata, Chordata, Animalia; Myoviridae: Viruses; Siphoviridae: Viruses

ORGN Organism Name
bacteriophage T4 (Myoviridae); endospore-forming gram-positive rods and cocci (Endospore-forming Gram-Positives); human (Hominidae); kidney bean (Leguminosae); rabbit (Leporidae); Bacillus subtilis (Endospore-forming Gram-Positives); Drosophila melanogaster (Diptera); Escherichia coli (Enterobacteriaceae); Saccharomyces cerevisiae (Ascomycetes); Siphoviridae (Siphoviridae); Synechococcus (Chroococcales)

ORGN Organism Superterms
angiosperms; animals; arthropods; bacteria; chordates; cyanobacteria; dicots; eubacteria; fungi; humans; insects; invertebrates; lagomorphs; mammals; microorganisms; nonhuman mammals; nonhuman vertebrates; nonvascular plants; plants; primates; spermatophytes; vascular plants; vertebrates; viruses

RN **9025-75-6** (PROTEIN PHOSPHATASE)
104987-11-3 (FK506)
59865-13-3Q (CYCLOSPORIN)
79217-60-0Q (CYCLOSPORIN)
56-45-1 (SERINE)
77238-39-2 (MICROCYSTIN)

L150 ANSWER 6 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:547426 BIOSIS
DN PREV199698561726
TI Preliminary **crystallization** studies of calmodulin-dependent protein phosphatase (**calcineurin**) from bovine brain.
AU Balendiran, K. (1); Tan, Yingchun; Sharma, Rajendra K.; Murthy, Krishna H. M. (1)
CS (1) Fels Inst. Cancer Res. Mol. Biol., Temple Univ. Sch. Med., 3307 North Broad Street, Allied Health Build, Room 557, Philadelphia, PA 19140 USA

SO Molecular and Cellular Biochemistry, (1995) Vol. 149-150, No. 0, pp. 127-130.
ISSN: 0300-8177.
DT Article
LA English
AB **Calcineurin** is a serine/threonine protein phosphatase which catalyzes the hydrolysis of both phosphoseryl/phosphothreonyl and phosphotyrosyl proteins as well as low molecular weight compounds such as p-nitrophenyl phosphate. It is a hetero-dimeric protein consisting of a 60 kDa A chain and 19 kDa B chain. **Calcineurin** A is organized into functionally distinct domains such as a catalytic domain, a **calcineurin** B binding domain, a calmodulin-binding domain, and an inhibitory domain. **Calcineurin** B has four EF-hand calcium binding domains with a secondary structure that is homologous to calmodulin but its metal binding properties are more similar to troponin-C. The N-terminal myristoyl group of **calcineurin** B might play a role in the interaction between subunits A and B during phosphorylation/dephosphorylation processes. **Crystals** of size 0.125 times 0.07 times 0.03 mm and 0.7 times 0.03 times 0.02 mm have been obtained for **calcineurin** and the A subunit respectively. **Crystals** of **calcineurin** show strong diffraction to 5.3 ANG and weak diffraction to 3.0 ANG on rotating anode operated at 50 kV and 100 mA. Further work is in progress to improve the X-ray diffraction quality of these **crystals** and to obtain well diffracting **crystals** of **calcineurin** B.
CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
BC Bovidae *85715
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
PROTEIN PHOSPHATASE; **CALCINEURIN**
IT Miscellaneous Descriptors
X-RAY DIFFRACTION
ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Bovidae (Bovidae)
ORGN Organism Superterms
animals; artiodactyls; chordates; mammals; nonhuman vertebrates; nonhuman mammals; vertebrates
RN **9025-75-6** (PROTEIN PHOSPHATASE)
9025-75-6 (**CALCINEURIN**)

L150 ANSWER 7 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:452387 BIOSIS
DN PREV199598466687
TI **Three-dimensional** structure of the catalytic subunit of protein serine/threonine phosphatase-1.
AU Goldberg, Jonathan; Huang, Hsien-Bin; Kwon, Young-Guen; Greengard, Paul; Nairn, Angus C.; Kuriyan, John (1)
CS (1) Howard Hughes Med. Inst., 1230 York Avenue, New York, NY 10021 USA
SO Nature (London), (1995) Vol. 376, No. 6543, pp. 745-753.
ISSN: 0028-0836.
DT Article
LA English
AB The **crystal** structure of mammalian protein phosphatase-1, complexed with the toxin microcystin and determined at 2.1 ANG resolution, reveals that It Is a metalloenzyme unrelated in architecture to the tyrosine phosphatases. Two metal Ions are positioned by a central beta-alpha-beta-alpha-beta scaffold at the active site, from which emanate three surface grooves that are potential binding sites for substrates and inhibitors. The carboxy terminus is positioned at the end of one of the grooves such that regulatory sequences following the domain might modulate

function. The fold of the catalytic domain is expected to be closely preserved in protein phosphatases 2A and 2B (**calcineurin**).
CC Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
SERINE; THREONINE; PROTEIN PHOSPHATASE
IT Miscellaneous Descriptors
PROTEIN PHOSPHATASE 2A; PROTEIN PHOSPHATASE 2B
RN 56-45-1 (SERINE)
72-19-5 (THREONINE)
9025-75-6 (PROTEIN PHOSPHATASE)

L150 ANSWER 8 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:443374 BIOSIS
DN PREV199598457674
TI Design, synthesis and structure on non-macrocyclic inhibitors of FKBP12, the major binding protein for the immunosuppressant FK506.
AU **Armistead, D. M. (1)**; Badia, M. C.; Deininger, D. D.; Duffy, J. P.; Sauders, J. O.; Tung, R. D.; **Thomson, J. A.**; Decenzo, M. T.; Futer, O.; Livingston, D. J.; Murcko, M. A.; Yamashita, M. M.; Navia, M. A. (1)
CS (1) Vertex Pharm. Inc., 40 Allston St., Cambridge, MA 02139-4211 USA
SO Acta Crystallographica Section D Biological Crystallography, (1995) Vol. 51, No. 4, pp. 522-528.
ISSN: 0907-4449.
DT Article
LA English
AB We have synthesized a series of non-macrocyclic ligands to FKBP12 that are comparable in binding potency and peptidyl prolyl isomerase (PPIase) inhibition to FK506 itself. We have also solved the structure of one of these ligands in complex with FKBP12, and have compared that structure to the FK506-FKBP12 complex. Consistent with the observed inhibitory equipotency of these compounds, we observe a strong similarity in the conformation of the two ligands in the region of the protein that mediates PPIase activity. Our compounds, however, are not immunosuppressive. In the FKBP12-FK506 complex, a significant portion of the FK506 ligand, its 'effector domain', projects beyond the envelope of the binding protein in a manner that is suggestive of a potential interaction with a second protein, the calcium-dependent phosphatase, **calcineurin**, whose inhibition by the FKBP12-FK506 complex interrupts the T-cell activation events leading to immunosuppression. In contrast, our compounds bind within the surface envelope of FKBP12, and induce significant changes in the structure of the FKBP12 protein which may also affect **calcineurin** binding indirectly.
CC Radiation - Radiation and Isotope Techniques 06504
Biochemical Methods - General 10050
Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - General Biophysical Techniques 10504
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Physiological Studies *10808
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Bovidae *85715
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Pharmacology
IT Chemicals & Biochemicals

FK506; ISOMERASE
IT Miscellaneous Descriptors
BINDING POTENCY; **CALCINEURIN**; ENZYME INHIBITION; FK506; IMMUNOSUPPRESSANT-DRUG; PEPTIDYL PROLYL ISOMERASE; STRUCTURE-BASED DRUG DESIGN; X-RAY **CRYSTALLOGRAPHY**
ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
cow (Bovidae)
ORGN Organism Superterms
animals; artiodactyls; chordates; mammals; nonhuman mammals; nonhuman vertebrates; vertebrates
RN 104987-11-3 (FK506)
9013-19-8 (ISOMERASE)

L150 ANSWER 9 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:443373 BIOSIS
DN PREV199598457673
TI Comparative X-ray structures of the major binding protein for the immunosuppressant FK506 (tacrolimus) in unligand form and in complex with FK506 and rapamycin.
AU **Wilson, Keith P.**; Yamashita, Mason M.; **Sintchak, Michael D.**; Rotstein, Sergio H.; Murcko, Mark A.; Boger, Joshua; **Thomson, John A.**; **Fitzgibbon, Matthew J.**; Black, James R.; Navia, Manuel A. (1)
CS (1) Vertex Pharm. Inc., 40 Allston St., Cambridge, MA 02139-4211 USA
SO Acta Crystallographica Section D Biological Crystallography, (1995) Vol. 51, No. 4, pp. 511-521.
ISSN: 0907-4449.
DT Article
LA English
AB FK506 (tacrolimus) is a natural product now approved in the US and Japan for organ transplantation. FK506, in complex with its 12 kDa cytosolic receptor (FKBP12), is a potent agonist of immunosuppression through the inhibition of the phosphatase activity of **calcineurin**. Rapamycin (sirolimus), which is itself an immunosuppressant by a different mechanism, completes with FK506 for binding to FKBP12 and thereby acts as an antagonist of **calcineurin** inhibition. We have solved the X-ray structure of unliganded FKBP12 and of FKBP12 in complex with FK506 and with rapamycin; these structures show localized differences in conformation and mobility in those regions of the protein that are known, by site-directed mutagenesis, to be involved in **calcineurin** inhibition. A comparison of 16 additional X-ray structures of FKBP12 in complex with FKBP12-binding ligands, where those structures were determined from different **crystal** forms with distinct packing arrangements, lends significance to the observed structural variability and suggests that it represents an intrinsic functional characteristic of the protein. Similar differences have been observed for FKBP12 before, but were considered artifacts of **crystal**-packing interactions. We suggest that immunosuppressive ligands express their differential effects in part by modulating the conformation of FKBP12, in agreement with mutagenesis experiments on the protein, and not simply through differences in the ligand structures themselves.
CC Radiation - Radiation and Isotope Techniques 06504
Biochemical Methods - General 10050
Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - General Biophysical Techniques 10504
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Physiological Studies *10808
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology 22005
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Bovidae 85715
Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Clinical Immunology (Human Medicine, Medical Sciences); Enzymology (Biochemistry and Molecular Biophysics); Pharmacology
IT Chemicals & Biochemicals
TACROLIMUS; FK506; RAPAMYCIN; **CALCINEURIN**
IT Miscellaneous Descriptors
CALCINEURIN INHIBITOR; FKBP12 PROTEIN; FK506; IMMUNOSUPPRESSANT-DRUG; PROTEIN CONFORMATION; RAPAMYCIN; STRUCTURE-BASED DRUG DESIGN; X-RAY **CRYSTALLOGRAPHY**
ORGN Super Taxa
Bovidae: Artiodactyla, Mammalia, Vertebrata, Chordata, Animalia; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
cow (Bovidae); human (Hominidae)
ORGN Organism Superterms
animals; artiodactyls; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; vertebrates
RN 104987-11-3 (TACROLIMUS)
104987-11-3 (FK506)
53123-88-9 (RAPAMYCIN)
9025-75-6 (**CALCINEURIN**)

L150 ANSWER 10 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:438130 BIOSIS
DN PREV199598452430
TI X-Ray Structure of **Calcineurin** Inhibited by the Immunophilin-Immunosuppressant FKBP-12-FK506 Complex.
AU **Griffith, James P.**; **Kim, Joseph L.**; **Kim, Eunice E.**; **Sintchak, Michael D.**; **Thomson, John A.**; **Fitzgibbon, Matthew J.**; **Fleming, Mark A.**; Caron, Paul R.; Hsiao, Kathy; Navia, Manuel A.
CS Vertex Pharmaceuticals Inc., 40 Allston Street, Cambridge, MA 02139-4211 USA
SO Cell, (1995) Vol. 82, No. 3, pp. 507-522.
ISSN: 0092-8674.
DT Article
LA English
AB The X-ray structure of the ternary complex of a **calcineurin** A fragment, **calcineurin** B, FKBP12, and the immunosuppressant drug FK506 (also known as tacrolimus) has been determined at 2.5 ANG resolution, providing a description of how FK506 functions at the atomic level. In the structure, the FKBP12-FK506 binary complex does not contact the phosphatase active site on **calcineurin** A that is more than 10 ANG removed. Instead, FKBP12-FK506 is so positioned that it can inhibit the dephosphorylation of its macromolecular substrates by physically hindering their approach to the active site. The ternary complex described here represents the **three-dimensional** structure of a Ser/Thr protein phosphatase and provides a structural basis for understanding **calcineurin** inhibition by FKBP12-FK506.
CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals *10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Pharmacology - Immunological Processes and Allergy *22018
Developmental Biology - Embryology - Morphogenesis, General *25508
Genetics of Bacteria and Viruses *31500
Virology - Animal Host Viruses *33506
Immunology and Immunochemistry - Bacterial, Viral and Fungal *34504
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
Medical and Clinical Microbiology - Virology *36006

Pharmacognosy and Pharmaceutical Botany *54000
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Development; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Immune System (Chemical Coordination and Homeostasis); Infection; Microbiology; Pharmacology
IT Chemicals & Biochemicals
CALCINEURIN; FK506; PHOSPHATASE
IT Sequence Data
amino acid sequence; molecular sequence data
IT Miscellaneous Descriptors
FK506; IMMUNOSUPPRESSANT-DRUG; MACROMOLECULAR SUBSTRATE DEPHOSPHORYLATION; PHARMACODYNAMICS; PHOSPHATASE ACTIVE SITE; TACROLIMUS
RN **9025-75-6 (CALCINEURIN)**
104987-11-3 (FK506)
9013-05-2 (PHOSPHATASE)

L150 ANSWER 11 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:421429 BIOSIS
DN PREV199598435729
TI Characterization of calmodulins containing the unnatural methionine analogs norleucine and ethionine.
AU Yuan, Tao; Vogel, Hans J.
CS Dep. Biol. Sci., Univ. Calgary, Calgary T2N 1N4 Canada
SO Protein Engineering, (1995) Vol. 8, No. SUPPL., pp. 37.
Meeting Info.: **Miami Bio/Technology Winter Symposium on Advances in Gene Technology: Protein Engineering and Structural Biology** Miami, Florida, USA February 4-9, 1995
ISSN: 0269-2139.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals *10069
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Enzymes - General and Comparative Studies; Coenzymes *10802
Physiology and Biochemistry of Bacteria *31000
Genetics of Bacteria and Viruses *31500
Food and Industrial Microbiology - General and Miscellaneous *39008
BC Enterobacteriaceae *06702
IT Major Concepts
Biochemistry and Molecular Biophysics; Bioprocess Engineering; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Membranes (Cell Biology); Methods and Techniques; Physiology
IT Chemicals & Biochemicals
NORLEUCINE; ETHIONINE; CALCIUM
IT Miscellaneous Descriptors
BETA-SHEET; BIOTECHNOLOGY; **CALCINEURIN**; CALCIUM-REGULATING PROTEIN; **CRYSTAL STRUCTURE**; GENE TECHNOLOGY; **MEETING ABSTRACT**; PROTEIN ENGINEERING; SIGNAL TRANSDUCTION; STRUCTURAL BIOLOGY; SYNTHETIC GENE; TARGET ENZYME
ORGN Super Taxa
Enterobacteriaceae: Eubacteria, Bacteria
ORGN Organism Name
Escherichia coli (Enterobacteriaceae)
ORGN Organism Superterms
bacteria; eubacteria; microorganisms
RN 327-57-1 (NORLEUCINE)
13073-35-3 (ETHIONINE)
7440-70-2 (CALCIUM)

L150 ANSWER 12 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1995:286493 BIOSIS
DN PREV199598300793
TI Identification of novel protein phosphatase 2A regulatory subunit.
AU Tehrani, M.; Mumby, M.; Kamibayashi, C.
CS Univ. Texas Southwestern Med. Cent., Dep. Pharmacol., Dallas, TX 75235-9041 USA
SO FASEB Journal, (1995) Vol. 9, No. 6, pp. A1346.
Meeting Info.: **Annual Meeting of the American Society for Biochemistry and Molecular Biology** San Francisco, California, USA May 21-25, 1995
ISSN: 0892-6638.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Methods *10804
Enzymes - Chemical and Physical *10806
BC Hominidae 86215
Muridae *86375
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques
IT Chemicals & Biochemicals
PROTEIN PHOSPHATASE
IT Miscellaneous Descriptors
ANALYTICAL METHOD; COMPLEMENTARY DNA; **MEETING ABSTRACT**; MESSENGER RNA; MOLECULAR **STRUCTURE**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); mouse (Muridae); rat (Muridae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 13 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:286492 BIOSIS
DN PREV199598300792
TI Characterization of human recombinant **calcineurin** heterodimer co-expressed in bacteria and insect cells.
AU Lewis, Cristina; Gastinel, Louis; Habuka, Noriyuki; Tucker, Kathleen; Chen, Xianghai; Maldonado, Fausto; Villafranca, J. E.
CS Agouron Pharm., San Diego, CA 92037 USA
SO FASEB Journal, (1995) Vol. 9, No. 6, pp. A1346.
Meeting Info.: **Annual Meeting of the American Society for Biochemistry and Molecular Biology** San Francisco, California, USA May 21-25, 1995
ISSN: 0892-6638.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - Immunological Processes and Allergy *22018
Developmental Biology - Embryology - Morphogenesis, General *25508
Physiology and Biochemistry of Bacteria 31000

Invertebrata, Comparative and Experimental Morphology, Physiology and Pathology - Insecta - Physiology *64076
BC Enterobacteriaceae 06702
Insecta - Unspecified 75300
Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Development; Enzymology (Biochemistry and Molecular Biophysics); Pharmacology
IT Chemicals & Biochemicals
CALCINEURIN
IT Miscellaneous Descriptors
ENZYME **STRUCTURE**; IMMUNOSUPPRESSIVE DRUGS; **MEETING ABSTRACT**; T-CELL PROLIFERATION
ORGN Super Taxa
Enterobacteriaceae: Eubacteria, Bacteria; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Insecta - Unspecified: Insecta, Arthropoda, Invertebrata, Animalia
ORGN Organism Name
Escherichia coli (Enterobacteriaceae); Hominidae (Hominidae); Insecta (Insecta - Unspecified)
ORGN Organism Superterms
animals; arthropods; bacteria; chordates; eubacteria; humans; insects; invertebrates; mammals; microorganisms; primates; vertebrates
RN **9025-75-6 (CALCINEURIN)**

L150 ANSWER 14 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:282675 BIOSIS
DN PREV199598296975
TI **Structure** of FK506 Bound to Triple Mutant FKBP13.
AU Lepre, Christopher (1); Futer, Olga; Livingston, David; Moore, Jonathan
CS (1) Vertex Pharm. Inc., Cambridge, MA 02139 USA
SO Journal of Cellular Biochemistry Supplement, (1995) Vol. 0, No. 21B, pp. 47.
Meeting Info.: **Keystone Symposium on Frontiers of NMR in Molecular Biology-IV** Keystone, Colorado, USA April 3-9, 1995
ISSN: 0733-1959.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Radiation - Radiation and Isotope Techniques 06504
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - General Biophysical Techniques *10504
Biophysics - Molecular Properties and Macromolecules *10506
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Mammalia - Unspecified *85700
IT Major Concepts
Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis); Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
FK506
IT Miscellaneous Descriptors
CALCINEURIN; IMMUNOSUPPRESSANT-DRUG; **MEETING ABSTRACT**; **MEETING POSTER**; NMR; NUCLEAR OVERHAUSER EFFECT; PHARMACODYNAMICS; PHARMACOKINETICS
ORGN Super Taxa
Mammalia - Unspecified: Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Mammalia (Mammalia - Unspecified)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals;

vertebrates
RN 104987-11-3 (FK506)

L150 ANSWER 15 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:243138 BIOSIS
DN PREV199598257438
TI **Structure**, regulation and function of serine/threonine protein kinases and phosphatases.
AU Nairn, Angus C.
CS Rockefeller Univ., New York, NY 10021 USA
SO Japanese Journal of Pharmacology, (1995) Vol. 67, No. SUPPL. 1, pp. 76P.
Meeting Info.: **68th Annual Meeting of the Japanese Pharmacological Society** Nagoya, Japan March 25-28, 1995
ISSN: 0021-5198.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Nervous System - Physiology and Biochemistry *20504
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Nervous System (Neural Coordination)
IT Chemicals & Biochemicals
SERINE; PHOSPHATASES; CALCIUM; PROTEIN KINASE; PROTEIN PHOSPHATASE
IT Miscellaneous Descriptors
CALCIUM/CALMODULIN-DEPENDENT PROTEIN KINASE; CENTRAL NERVOUS SYSTEM; **MEETING ABSTRACT**; SIGNAL TRANSDUCTION; TYPE I PROTEIN PHOSPHATASE
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 56-45-1 (SERINE)
9013-05-2D (PHOSPHATASES)
7440-70-2 (CALCIUM)
9026-43-1 (PROTEIN KINASE)
9025-75-6 (PROTEIN PHOSPHATASE)

L150 ANSWER 16 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:131166 BIOSIS
DN PREV199598145466
TI **Three-dimensional** structure and actions of immunosuppressants and their immunophilins.
AU Braun, Werner; Kallen, Joerg; Mikol, Vincent; Walkinshaw, Malcolm D. (1); Wuethrich, Kurt
CS (1) Preclin. Res., Sandoz Pharma Ltd., 4002 Basel Switzerland
SO FASEB Journal, (1995) Vol. 9, No. 1, pp. 63-72.
ISSN: 0892-6638.
DT Article
LA English
AB The use of the immunosuppressant drug cyclosporin A (CsA) as a biochemical tool to study the signal transduction pathway in T cells has led to the discovery of a first family of immunosuppressant-binding proteins or "immunophilins" the cyclophilins (Cyp). Another, chemically unrelated immunosuppressant molecule, FK506, was then found to be related to a second class of immunophilins, the FK506-binding proteins (FKBPs). This paper reviews the existing structural information on these immunophilins in the context of present knowledge of the biochemical mechanisms for immunosuppression. The formation of Cyp-CsA and FKBP-FK506 complexes, and

the subsequent specific interaction of these complexes with the serine/threonine phosphatase **calcineurin** (CN), are key steps in the cascade of events that result in the desired immunosuppression. Knowledge of the conformation of the Cyp-CsA-CN and FKBP-FK506-CN ternary complexes is of significant biomedical interest, because mimics of the composite contact surfaces of, for example, Cyp-CsA or FKBP-FK506, could provide immunosuppressant drugs with improved pharmacological profiles.

CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Vertebrata - Unspecified *85150

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Immune System (Chemical Coordination and Homeostasis); Pharmacology

IT Chemicals & Biochemicals
CYCLOSPORIN A; FK506

IT Miscellaneous Descriptors
CYCLOPHILIN; CYCLOSPORIN A; FK506; IMMUNOSUPPRESSANT-BINDING PROTEIN; MOLECULAR MODELING; T-CELLS

ORGN Super Taxa
Vertebrata - Unspecified: Vertebrata, Chordata, Animalia

ORGN Organism Name
Vertebrata (Vertebrata - Unspecified)

ORGN Organism Superterms
animals; chordates; nonhuman vertebrates; vertebrates

RN 59865-13-3 (CYCLOSPORIN A)
104987-11-3 (FK506)

L150 ANSWER 17 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1995:131066 BIOSIS

DN PREV199598145366

TI **Crystal structures** of cyclophilin A complexed with cyclosporin A and N-methyl-4-((E)-2-butenyl)-4,4-dimethylthreonine cyclosporin A.

AU Ke, Hengming (1); Mayrose, Dale; Belshaw, Peter J.; Albery, David G.; Schreiber, Stuart L.; Chang, Zhi Yuh; Etzkorn, Felicia A.; Ho, Susanna; Walsh, Christopher T.

CS (1) Dep. Biochem. Biophysics, Sch. Med., Univ. North Carolina, Chapel Hill, NC 27599 USA

SO Structure (London), (1994) Vol. 2, No. 1, pp. 33-44.
ISSN: 0969-2126.

DT Article

LA English

AB Background: Cyclophilin (CyP) is a ubiquitous intracellular protein that binds the immunosuppressive drug cyclosporin A (CsA). CyP-CsA forms a ternary complex with **calcineurin** and thereby inhibits T-cell activation. CyP also has enzymatic activity, catalyzing the cis-trans isomerization of peptidyl-prolyl amide bonds. Results: We have determined the structure of human cyclophilin A (CyPA) complexed with CsA to 2.1 ANG resolution. We also report here the structure of CyPA complexed with an analog of CsA, N-methyl-4-((E)2-butenyl)-4,4-dimethylthreonine CsA (MeBm-2t1-CsA), which binds less well to CyPA, but has increased immunosuppressive activity. Comparison of these structures with previously determined structures of unligated CyPA and CyPA complexed with a candidate substrate for the isomerase activity, the dipeptide AlaPro, reveals that subtle conformational changes occur in both CsA and CyPA on complex formation. Conclusions: MeBm-2t1-CsA binds to CyPA in an essentially similar manner to CsA. The 100-fold weaker affinity of its binding may be attributable to the close contact between MeBmt1 and the active site residue Ala103 of CyPA, which causes small conformational

changes in both protein and drug. One change, the slight movement of MeLeu6 in CsA relative to MeBm-2t1-CsA, may be at least partially responsible for the higher affinity of the CyPA-MeBm-2t1-CsA complex for **calcineurin**. Our comparison between CyPA-CsA and CyPA-AlaPro suggests that CsA is probably not an analog of the natural substrate, confirming that the catalytic activity of CyPA is not related to its role in immunosuppression either structurally or functionally.

CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Pharmacology - General *22002
Pharmacology - Immunological Processes and Allergy *22018

BC Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Pharmacology

IT Chemicals & Biochemicals
CYCLOSPORIN A

IT Miscellaneous Descriptors
ACTIVE SITE RESIDUE; **CALCINEURIN**; DRUG DESIGN; IMMUNOSUPPRESSANT AGENT; MOLECULAR MODELING; SUBSTRATE AFFINITY; **THREE-DIMENSIONAL** STRUCTURE

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
human (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN 59865-13-3 (CYCLOSPORIN A)

L150 ANSWER 18 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1995:123588 BIOSIS

DN PREV199598137888

TI Predicted Secondary and Supersecondary Structure for the Serine-Threonine-Specific Protein Phosphatase Family.

AU Jenny, Thomas F.; Gerloff, Dietlind L.; Cohen, Mark A.; Benner, Steven A. (1)

CS (1) Dep. Chem., ETH, CH-8092 Zurich Switzerland

SO Proteins Structure Function and Genetics, (1995) Vol. 21, No. 1, pp. 1-10. ISSN: 0887-3585.

DT Article

LA English

AB A bona fide consensus prediction for the secondary and supersecondary structure of the serine-threonine specific protein phosphatases is presented. The prediction includes assignments of active site segments, an internal helix, and a region of possible 3-10 helical structure. An experimental structure for a member of this family of proteins should appear shortly, allowing this prediction to be evaluated.

CC Evolution *01500
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806

IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Evolution and Adaptation

IT Chemicals & Biochemicals
SERINE; PROTEIN PHOSPHATASE

IT Sequence Data
amino acid sequence; molecular sequence data

IT Miscellaneous Descriptors
ACTIVE SITE; INTERNAL HELIX; MOLECULAR EVOLUTION; **THREE-DIMENSIONAL** STRUCTURE

RN 56-45-1 (SERINE)
9025-75-6 (PROTEIN PHOSPHATASE)

L150 ANSWER 19 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1995:73203 BIOSIS
DN PREV199598087503
TI The molecular replacement solution and X-ray refinement to 2.8 A of a decameric complex of human cyclophilin A with the immunosuppressive drug cyclosporin A.
AU Pflugl, Gaston M. (1); Kallen, Jorg; Jansonius, Johan N.; Walkinshaw, Malcolm D.
CS (1) Mol. Biol. Inst., UCLA, 405 Hilgard Ave., Los Angeles, CA 90024-1570 USA
SO Journal of Molecular Biology, (1994) Vol. 244, No. 4, pp. 385-409. ISSN: 0022-2836.
DT Article
LA English
AB The X-ray structure of a decameric form of a complex of human cyclophilin A (CypA) with the immunosuppressive drug cyclosporin A (CsA) has been determined. The **crystals** of space group P4-32-12 with cell dimensions a = b = 95.2 ANG , c = 280.0 ANG have five copies of the cyclophilin A/cyclosporin A complex in the asymmetric unit. The structure was solved by molecular replacement techniques, using a known cyclophilin A model. Procedures were developed to construct a self-rotation function using the results of cross-rotation searches. The comparison of experimental and constructed self-rotation maps was an important aid in selecting the correct rotation function solution. The translation functions revealed the presence of a cyclic pentamer. A **crystallographic** dimer axis passes through the non-**crystallographic** 5-fold rotation axis of the pentameric asymmetric unit, and generates a decameric "sandwich" of CypA/CsA heterodimers that has 52 symmetry. The five CypA/CsA protomers were refined independently using all data to 2.8 ANG giving a final **crystallographic** R-factor of 15.7%. Despite the constraints due to the packing arrangement within the decamer, the CypA and CsA conformations are similar to other CypA/CsA structures determined by X-ray **crystallography** and NMR spectroscopy. The hydrophobic CsA molecules are embedded in the middle of the decameric sandwich with only 20% of their surface exposed to solvent. The binding loop of CsA (residues 1 to 3 and 9 to 11) comprising 42% of the CsA surface, is buried in the peptidyl-prolyl-cis-trans isomerase active site of the cognate binding partner CypA, while the effector loops (residues 4 to 8) packs in the core of the decamer making hydrogen-bonding and van der Waals contacts with three neighbouring molecules. The environment of CsA in the decamer has been analysed and may provide a mimic for the interactions likely to occur between the CypA/CsA complex and its biological target **calcineurin**. There is no evidence to suggest that the decameric sandwich itself plays a role in immunosuppression by inhibiting **calcineurin**. However, the chaperone/foldase activity of CypA could require oligomer formation for its biological function.
CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Pharmacology - Clinical Pharmacology *22005
Pharmacology - Immunological Processes and Allergy *22018
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Pharmacology
IT Chemicals & Biochemicals
CYCLOSPORIN A; PEPTIDYL-PROPYL-CIS-TRANS ISOMERASE
IT Miscellaneous Descriptors
CALCINEURIN; CHAPERONE-FOLDASE ACTIVITY; NMR SPECTROSCOPY; PEPTIDYL-PROPYL-CIS-TRANS ISOMERASE; PROTEIN **CRYSTAL** STRUCTURE; SELF-ROTATION FUNCTION; X-RAY **CRYSTALLOGRAPHY**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 59865-13-3 (CYCLOSPORIN A)
95076-93-0 (PEPTIDYL-PROPYL-CIS-TRANS ISOMERASE)

L150 ANSWER 20 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:68216 BIOSIS
DN PREV199598082516
TI Solution structure of FK506 bound to the R42K, H87V double mutant of FKBP-12.
AU Lepre, Christopher A.; Pearlman, David A.; Cheng, Jya-Wei; Decenzo, Maureen T.; Livingston, David J.; Moore, Jonathan M. (1)
CS (1) Vertex Pharmaceuticals Incorporated, 40 Allston Street, Cambridge, MA 02139-4211 USA
SO Biochemistry, (1994) Vol. 33, No. 46, pp. 13571-13580.
ISSN: 0006-2960.
DT Article
LA English
AB The binding of the FK506/FKBP-12 complex to **calcineurin** (CN), its putative target for immunosuppression, involves recognition of solvent-exposed regions of the ligand as well as FKBP-12 residues near the active site. The R42K, H87V double mutation of FKBP-12 decreases the CN affinity of the complex by 550-fold (Aldape, R. A., Futer, O., DeCenzo, M. T., Jarrett, B. P., Murcko, M. A., & Livingston, D. J. (1992) J. Biol. Chem. 267, 16029-16032). This work reports the solution structure of 13C-labeled FK506 bound to R42K. H87V FKBP-12. Assignments and NOE measurements at three mixing times were made from inverse-detected 1H-13C NMR experiments. Structures were calculated by several different methods, including distance geometry, restrained molecular dynamics, and molecular dynamics with time-averaged restraints. The NMR structures of the ligand and are very well defined by the NOE restraints and differ slightly from the X-ray structure in regions that are involved in **crystal** packing. Comparison with the NMR structure of FK506 bound to wild-type FKBP-12 reveals that the R42K, H87V mutation causes the ligand backbone near C16 to move by 2.5 to 45 ANG , reorients 15-MeO by 90 degree , and shifts 13-MeO by approximately 1.5 ANG . FK506 appears to undergo to undergo a concerted, mutational)%, induced shift in the binding pocket, with the greatest changes occurring in the effector region of the drug. The altered effector conformation of mutant-bound FK506 may perturb interactions between the drug and CN, thus accounting for the effect of the double mutation upon the CN inhibitory activity of the complex.
CC Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Metabolism - Proteins, Peptides and Amino Acids *13012
Pharmacology - Immunological Processes and Allergy *22018
IT Major Concepts
Biochemistry and Molecular Biophysics; Metabolism; Pharmacology
IT Chemicals & Biochemicals
FK506; **CALCINEURIN**
IT Miscellaneous Descriptors
CALCINEURIN ACTIVITY; FK506; FK506 BINDING PROTEIN; IMMUNOSUPPRESSANT-DRUG
RN 104987-11-3 (FK506)
9025-75-6 (CALCINEURIN)

L150 ANSWER 21 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:63217 BIOSIS
DN PREV199598077517
TI Mapping of the gene for rat protein phosphatase 2C-alpha (PP2C1) to Chromosome 6.
AU Yamada, T. (1); Muramatsu, Y.; **Kim, J. K.**; Serikawa, T.; Matsumoto, K.
CS (1) Inst. Anim. Exp., Univ. Tokushima Sch. Med., Tokushima Japan
SO Mammalian Genome, (1994) Vol. 5, No. 10, pp. 655-656.
ISSN: 0938-8990.

DT Article
LA English
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Chemical and Physical *10806
BC Hominidae 86215
Muridae *86375
IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics
IT Chemicals & Biochemicals
PROTEIN PHOSPHATASE
IT Miscellaneous Descriptors
GENE HOMOLOGY; NOTE; PROTEIN PHOSPHATASE 2C-ALPHA; SP-2 CELLS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); mouse (Muridae)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman mammals; nonhuman vertebrates; primates; rodents; vertebrates
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 22 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1995:25736 BIOSIS
DN PREV199598040036
TI The latch region of **calcineurin** B is involved in both immunosuppressant-immunophilin complex docking and phosphatase activation.
AU Milan, David (1); **Griffith**, **Jim**; Su, Michael; Price, E. Roydon (1); McKeon, Frank (1)
CS (1) Dep. Cell Biol., Harv. Med. Sch., Boston, MA 02115 USA
SO Cell, (1994) Vol. 79, No. 3, pp. 437-447.
ISSN: 0092-8674.
DT Article; General Review
LA English
AB The immunosuppressants cyclosporin A and FK506, when complexed with their intracellular receptors, prevent T cell activation by directly binding to the phosphatase **calcineurin**. We have used molecular modeling and mutagenesis to identify sites on **calcineurin** important for this interaction. We have created **calcineurins** that are resistant to both cyclosporin A and FK506 by mutating specific residues in CnB, a calcium-binding protein that regulates the catalytic subunit, CnA. Significantly, on a model of CnB, these mutations map to the latch region, an element of tertiary structure that forms when CnB binds CnA. In addition, we show that this latch region plays an important role in activating the catalytic subunit CnA. These results suggest a molecular mechanism for suppression of **calcineurin** by cyclosporin A and FK506 involving their binding to the same region of CnB used for allosterically activating CnA.
CC Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Enzymes - Physiological Studies *10808
Pathology, General and Miscellaneous - Therapy *12512
Metabolism - Proteins, Peptides and Amino Acids *13012
Pharmacology - Clinical Pharmacology 22005
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Enterobacteriaceae 06702
Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Clinical Immunology (Human Medicine, Medical Sciences); Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Metabolism; Pathology; Pharmacology
IT Chemicals & Biochemicals
CALCINEURIN; PHOSPHATASE; CYCLOSPORIN A; FK 506
IT Miscellaneous Descriptors
CYCLOSPORIN A; FK 506; IMMUNOSUPPRESSANT-DRUG; MOLECULAR INTERACTION; MOLECULAR MODELLING; MUTAGENESIS; PHARMACODYNAMICS; USE
ORGN Super Taxa
Enterobacteriaceae: Eubacteria, Bacteria; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); Escherichia coli (Enterobacteriaceae)
ORGN Organism Superterms
animals; bacteria; chordates; eubacteria; humans; mammals; microorganisms; primates; vertebrates
RN **9025-75-6 (CALCINEURIN)**
9013-05-2 (PHOSPHATASE)
59865-13-3 (CYCLOSPORIN A)
104987-11-3 (FK 506)

L150 ANSWER 23 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:358171 BIOSIS
DN PREV199497371171
TI Chromosomal assignments of the genes for the **calcineurin** A-alpha (Calna1) and A-beta subunits (Calna2) in the rat.
AU Yamada, T.; **Kim, J. K.**; Muramatsu, Y.; Serikawa, T.; Matsumoto, K. (1)
CS (1) Inst. Animal Experimentation, Univ. Tokushima Sch. Med., Kuramoto 3, Tokushima 770 Japan
SO Cytogenetics and Cell Genetics, (1994) Vol. 67, No. 1, pp. 55-57. ISSN: 0301-0171.
DT Article
LA English
AB Chromosomal assignments of the genes for the **calcineurin** A-alpha (Calna1) and A-beta (Calna2) subunits in the rat genome were performed by polymerase chain reaction/single strand conformation polymorphism (PCR/SSCP) analysis of somatic cell hybrid DNAs. Both genes, Calna1 and Calna2, were assigned to rat chromosome 15.
CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Chemical and Physical *10806
BC Muridae *86375
IT Major Concepts
Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics
IT Chemicals & Biochemicals
CALCINEURIN
IT Miscellaneous Descriptors
DNA; GENE MAPPING; POLYMERASE CHAIN REACTION/SINGLE-STRAND CONFORMATION POLYMORPHISM
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates
RN **9025-75-6 (CALCINEURIN)**

L150 ANSWER 24 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:301221 BIOSIS

DN PREV199497314221
TI X-ray structure of a cyclophilin B/cyclosporin complex: Comparison with cyclophilin A and delineation of its **calcineurin**-binding domain.
AU Mikol, Vincent; Kallen, Jorg; Walkinshaw, Malcolm D.
CS Preclin. Res., Sandoz AG, CH-4002 Basel Switzerland
SO Proceedings of the National Academy of Sciences of the United States of America, (1994) Vol. 91, No. 11, pp. 5183-5186.
ISSN: 0027-8424.
DT Article
LA English
AB The **crystal** structure of a complex between recombinant human cyclophilin B (CypB) and a cyclosporin A (CsA) analog has been determined and refined at 1.85- ANG resolution to a **crystallographic** R factor of 16.0%. The overall structures of CypB and of cyclophilin A (CypA) are similar; however, significant differences occur in two loops and at the N and C termini. The CsA-binding pocket in CypB has the same structure as in CypA and cyclosporin shows a similar bound conformation and network of interactions in both CypB and CypA complexes. The network of the water-mediated contacts is also essentially conserved. The higher potency of the CypB/CsA complex versus CypA/CsA in inhibiting the Ca-2+and calmodulin-dependent protein phosphatase **calcineurin** is discussed in terms of the structural differences between the two complexes. The three residues Arg-90, Lys-113, and Ala-128 and the loop containing Arg-158 on the surface of CypB are likely to modulate the differences in **calcineurin** inhibition between CypA and CypB.
CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Immunology and Immunochemistry - General; Methods *34502
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Immune System (Chemical Coordination and Homeostasis); Morphology
IT Chemicals & Biochemicals
CYCLOSPORIN
IT Miscellaneous Descriptors
IMMUNOPHILIN; PROTEIN **CRYSTALLOGRAPHY**
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 59865-13-3QD (CYCLOSPORIN)
79217-60-0QD (CYCLOSPORIN)

L150 ANSWER 25 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:224345 BIOSIS
DN PREV199497237345
TI 1H, 13C, 15N nuclear magnetic resonance backbone assignments and secondary structure of human **calcineurin** B.
AU Anglister, Jacob (1); Grzesiek, Stephan; Wang, Andy C.; Ren, Hao; Klee, Claude B.; Bax, Ad (1)
CS (1) Lab. Chem. Physics, Natl. Inst. Diabetes Digestive and Kidney Dis., Bethesda, MD 20892 USA
SO Biochemistry, (1994) Vol. 33, No. 12, pp. 3540-3547.
ISSN: 0006-2960.
DT Article
LA English
AB The calmodulin- and calcium-stimulated protein phosphatase **calcineurin**, PP2B, consists of two subunits: **calcineurin** B, which binds Ca-2+, and **calcineurin** A, which contains the catalytic site and a calmodulin binding site. Heteronuclear 3D and 4D NMR experiments were carried out on a recombinant human **calcineurin** B which is a 170-residue protein of molecular mass 19.3 kDa, uniformly

labeled with 15N and 13C. The nondenaturing detergent CHAPS was used to obtain a monomeric form of **calcineurin** B. **Three-dimensional** triple resonance experiments yielded complete sequential assignment of the backbone nuclei (1H, 13C, and 15N). This assignment was verified by a 4D HN(COCA)NH experiment carried out with 50% randomly deuteriated and uniformly 15N-and 13C-enriched **calcineurin** B. The secondary structure of **calcineurin** B has been determined on the basis of the 13C-alpha and 13C-beta secondary chemical shifts, J(H-NH-alpha) couplings, and NOE connectivities obtained from 3D 15N-separated and 4D 13C/15N-separated NOESY spectra. **Calcineurin** B has eight helices distributed in four EF-hand, helix-loop-helix (Kretsinger, R. H. (1980) CRC Crit. Rev. Biochem. 8, 119-174) calcium binding domains. The secondary structure of **calcineurin** B is highly homologous to that of calmodulin. In comparison to calmodulin, helices B and C are shorter while helix G is considerably longer. As was observed for calmodulin in solution, **calcineurin** B does not have a single long central helix; rather, helices D and E are separated by a six-residue sequence in a flexible nonhelical conformation.

CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals 10069
Biophysics - General Biophysical Techniques *10504
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012

BC Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Metabolism; Methods and Techniques

IT Chemicals & Biochemicals
CALCINEURIN; CALCIUM; PROTEIN PHOSPHATASE

IT Miscellaneous Descriptors
CALCIUM-STIMULATED PROTEIN PHOSPHATASE; CALMODULIN; MACROMOLECULAR STRUCTURE; NMR

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

RN **9025-75-6** (**CALCINEURIN**)
7440-70-2 (CALCIUM)
9025-75-6 (PROTEIN PHOSPHATASE)

L150 ANSWER 26 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1994:216381 BIOSIS

DN PREV199497229381

TI **Three-dimensional** solution structure of Escherichia coli periplasmic cyclophilin.

AU Clubb, Robert T.; Ferguson, Stephen B.; Walsh, Christopher T.; Wagner, Gerhard (1)

CS (1) Dep. Biological Chem. and Mol. Pharmacol., Harvard Med. Sch., 240 Longwood Ave., Boston, MA 02115 USA

SO Biochemistry, (1994) Vol. 33, No. 10, pp. 2761-2772.
ISSN: 0006-2960.

DT Article

LA English

AB The solution structure of the periplasmic cyclophilin type cis-trans peptidyl-prolyl isomerase from Escherichia coli (167 residues, MW gt 18.200) has been determined using multidimensional heteronuclear NMR spectroscopy and distance geometry calculations. The structure determination is based on a total of 1720 NMR-derived restraints (1566 distance and 101 vphi and 53 chi-1 torsion angle restraints). Twelve distance geometry structures were calculated, and the average root-mean-square (rms) deviation about the mean backbone coordinate positions is 0.84 +- 0.18 ANG for the backbone atoms of residues 5-165 of

the ensemble. The **three-dimensional** structure of E. coli cyclophilin consists of an eight-stranded antiparallel beta-sheet barrel capped by alpha-helices. The average coordinates of the backbone atoms of the core residues of E. coli cyclophilin have an rms deviation of 1.44 A, with conserved regions in the **crystal** structure of unligated human T cell cyclophilin (Ke, H. (1992) J. Mol. Biol. 228, 539-550). Four regions proximal to the active site differ substantially and may determine protein substrate specificity, sensitivity to cyclosporin A, and the composite drug:protein surface required to inhibit **calcineurin**. A residue essential for isomerase activity in human T cell cyclophilin (His 126) is replaced by Tyr 122 in E. coli cyclophilin without affecting enzymatic activity.

CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Physiology and Biochemistry of Bacteria *31000
BC Enterobacteriaceae *06702
IT Major Concepts
Biochemistry and Molecular Biophysics; Physiology
IT Miscellaneous Descriptors
MOLECULAR STRUCTURE
ORGN Super Taxa
Enterobacteriaceae: Eubacteria, Bacteria
ORGN Organism Name
Escherichia coli (Enterobacteriaceae)
ORGN Organism Superterms
bacteria; eubacteria; microorganisms

L150 ANSWER 27 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:197222 BIOSIS
DN PREV199497210222
TI Cyclosporins: **Structure**-activity relationships.
AU Fliri, Hans; Baumann, Goetz; Enz, Albert; Kallen, Juerg; Luyten, Marcel; Mikol, Vincent; Movva, Rao; Quesniaux, Valerie; Schreier, Max; et al.
CS Sandoz Pharma AG, Preclinical Res. Lab., CH-4002 Basel Switzerland
SO Allison, A. C. [Editor]; Lafferty, K. J. [Editor]; Fliri, H. [Editor]. Annals of the New York Academy of Sciences, (1993) Vol. 696, pp. 47-53. Annals of the New York Academy of Sciences; Immunosuppressive and antiinflammatory drugs.
Publisher: New York Academy of Sciences 2 East 63rd Street, New York, New York 10021, USA.
Meeting Info.: **Conference** Orlando, Florida, USA April 12-15, 1993
ISSN: 0077-8923. ISBN: 0-89766-836-7 (paper), 0-89766-835-9 (cloth).
DT Book; **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Methods - General *10050
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Pathology, General and Miscellaneous - Therapy 12512
Pharmacology - General *22002
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Clinical Pharmacology 22005
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Clinical Immunology (Human Medicine, Medical Sciences); Enzymology (Biochemistry and Molecular Biophysics); Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
CYCLOSPORINS; CYCLOSPORIN A

IT Miscellaneous Descriptors
BOOK CHAPTER; **CALCINEURIN**; CYCLOSPORIN A;
CYCLOSPORIN-CYCLOPHILIN COMPLEX; IMMUNOSUPPRESSANT-DRUG;
MEETING PAPER; PHARMACODYNAMICS
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 59865-13-3QD (CYCLOSPORINS)
79217-60-0QD (CYCLOSPORINS)
59865-13-3 (CYCLOSPORIN A)

L150 ANSWER 28 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:130877 BIOSIS
DN PREV199497143877
TI Increased production of paired helical filament epitopes in a cell culture system reduces the turnover of tau.
AU Vincent, Inez (1); Rosado, Michelle; **Kim, Elaine**; Davies, Peter
CS (1) Dep. Pathol., Albert Einstein Coll. Med., F526, 1300 Morris Park Ave., Bronx, NY 10461 USA
SO Journal of Neurochemistry, (1994) Vol. 62, No. 2, pp. 715-723.
ISSN: 0022-3042.
DT Article
LA English
AB To investigate the regulation of posttranslational modifications of tau that might be pertinent to the production of the paired helical filament (PHF) of Alzheimer's disease, we incubated human neuroblastoma cells with the protein phosphatase inhibitor okadaic acid. This treatment results in increased immunoreactivity of tau with the monoclonal antibodies Alz-50, PHF-1, T3P, and NP8, a reduction in Tau-1 immunoreactivity, and an elevation in apparent molecular weight of tau. Moreover, our data demonstrate that accumulation of phosphates in tau leads to a decrease in the turnover rate of tau in the neuroblastoma cells. It is suggested that similar build-up of hyperphosphorylated tau in the neuronal perikarya may represent an early event in PHF formation. The present system facilitates the investigation of regulatory mechanisms governing the occurrence of PHF epitopes, their effects on neuronal cell metabolism, and possible pharmacological intervention.
CC Cytology and Cytochemistry - Human *02508
Behavioral Biology - Human Behavior *07004
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Nervous System - Pathology *20506
Psychiatry - Psychopathology; Psychodynamics and Therapy *21002
Immunology and Immunochemistry - General; Methods *34502
BC Hominidae *86215
IT Major Concepts
Behavior; Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Metabolism; Neurology (Human Medicine, Medical Sciences); Psychiatry (Human Medicine, Medical Sciences)
IT Chemicals & Biochemicals
OKADAIC ACID; PROTEIN PHOSPHATASE
IT Miscellaneous Descriptors
ALZHEIMER'S DISEASE; IMMUNOREACTIVITY; NEURON; OKADAIC ACID; PROTEIN PHOSPHATASE 2A; PROTEIN PHOSPHORYLATION
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae)
ORGN Organism Superterms

animals; chordates; humans; mammals; primates; vertebrates
RN 78111-17-8 (OKADAIC ACID)
9025-75-6 (PROTEIN PHOSPHATASE)

L150 ANSWER 29 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:125646 BIOSIS
DN PREV199497138646
TI Co-**crystallization** of the catalytic subunit of the serine/threonine specific protein phosphatase 1 from human in complex with microcystin LR.
AU Barford, David (1); Keller, James C.
CS (1) W. M. Keck Structural Biol. Lab., Cold Spring Harbor Lab., Cold Spring Harbor, P.O. Box 100, NY 11724 USA
SO Journal of Molecular Biology, (1994) Vol. 235, No. 2, pp. 763-766. ISSN: 0022-2836.
DT Article
LA English
AB The catalytic subunit of the serine/threonine specific protein phosphatase 1 from human (molecular mass 37 KDa) has been co-**crystallized** in complex with the cyanobacterial toxin microcystin LR (molecular mass 1 kDa). The **crystals** diffract to a resolution of 2.8 ANG when exposed to synchrotron radiation and belong to space group P2-12-12 with a = 109.5 ANG , b = 90.6 ANG , c = 38.7 ANG . There is one molecule of protein phosphatase 1 per asymmetric unit. The **crystal** form is suitable for the determination of the atomic structure of protein phosphatase 1.
CC Cytology and Cytochemistry - Human *02508
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Enzymes - Methods *10804
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Methods and Techniques
IT Chemicals & Biochemicals
SERINE; THREONINE; PROTEIN PHOSPHATASE; MICROCYSTIN LR
IT Miscellaneous Descriptors
MOLECULAR BIOLOGY; SIGNAL TRANSDUCTION
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 56-45-1 (SERINE)
72-19-5 (THREONINE)
9025-75-6 (PROTEIN PHOSPHATASE)
101043-37-2 (MICROCYSTIN LR)

L150 ANSWER 30 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1994:23278 BIOSIS
DN PREV199497036278
TI Structure-based design of a cyclophilin-**calcineurin** bridging ligand.
AU Alberg, David G.; Schreiber, Stuart L. (1)
CS (1) Dep. Chem., Harvard Univ., Cambridge, MA 02138 USA
SO Science (Washington D C), (1993) Vol. 262, No. 5131, pp. 248-250. ISSN: 0036-8075.
DT Article
LA English
AB The affinity of a flexible ligand that adopts a specific conformation when

bound to its receptor should be increased with the appropriate use of conformational restraints. By determining the structure of protein-ligand complexes, such restraints can in principle be designed into the bound ligand in a rational way. A tricyclic variant (TCsA) of the immunosuppressant cyclosporin A (CsA), which inhibits the proliferation of T lymphocytes by forming a cyclophilin-CsA-**calcineurin** complex, was designed with the known **three-dimensional** structure of a cyclophilin-CsA complex. The conformational restraints in TCsA appear to be responsible for its greater affinity for cyclophilin and **calcineurin** relative to CsA.

CC Cytology and Cytochemistry - Human *02508
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Pathology, General and Miscellaneous - Therapy *12512
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Pharmacology - General *22002
Pharmacology - Clinical Pharmacology 22005
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - Immunopathology, Tissue Immunology *34508

BC Hominidae *86215

IT Major Concepts
Biochemistry and Molecular Biophysics; Blood and Lymphatics (Transport and Circulation); Cell Biology; Clinical Immunology (Human Medicine, Medical Sciences); Membranes (Cell Biology); Pathology; Pharmacology

IT Miscellaneous Descriptors
CYCLOPHILIN-**CALCINEURIN**; HUMAN USE; IMMUNOSUPPRESSANT-DRUG; MOLECULAR CONFORMATION; PHARMACODYNAMICS; STRUCTURE-ACTIVITY RELATIONSHIP; T-LYMPHOCYTE PROLIFERATION

ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia

ORGN Organism Name
Hominidae (Hominidae)

ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates

L150 ANSWER 31 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS

AN 1993:477178 BIOSIS

DN PREV199396110778

TI Expression, purification, **crystallization**, and biochemical characterization of a recombinant protein phosphatase.

AU Zhuo, Shaoqui; Clemens, James C.; Hakes, David J.; Barford, David; Dixon, Jack E. (1)

CS (1) Dep. Biol. Chem., University Michigan Med. Sch., 5416 Medical Sci. I, Ann Arbor, MI 48109-0606 USA

SO Journal of Biological Chemistry, (1993) Vol. 268, No. 24, pp. 17754-17761. ISSN: 0021-9258.

DT Article

LA English

AB A protein phosphatase (PPase) from the bacteriophage lambda was overexpressed in Escherichia coli. The recombinant enzyme was purified to homogeneity yielding approximately 17 mg of enzyme from a single liter of bacterial culture. Biochemical characterization of the enzyme showed that it required Mn-2+ or Ni-2+ as an activator. The recombinant enzyme was active toward serine, threonine, and tyrosine phosphoproteins and phosphopeptides. Surprisingly, the bacterial histidyl phosphoprotein, NR-II, was also dephosphorylated by the lambda-PPase. The lambda-PPase shares a number of kinetic and structural properties with the eukaryotic Ser/Thr phosphatases, suggesting that the lambda-PPase will serve as a good model for structure-function studies. **Crystallization** of the recombinant purified lambda-PPase yielded monoclinic **crystals** . The **crystals** diffract to 4.0 ANG when exposed to synchrotron

x-ray radiation.
CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Physiology and Biochemistry of Bacteria *31000
BC Enterobacteriaceae *06702
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Physiology
IT Chemicals & Biochemicals
PROTEIN PHOSPHATASE; SERINE; THREONINE; TYROSINE
IT Miscellaneous Descriptors
6=FLUORO-L-TRYPTOPHAN
ORGN Super Taxa
Enterobacteriaceae: Eubacteria, Bacteria
ORGN Organism Name
Enterobacteriaceae (Enterobacteriaceae)
ORGN Organism Superterms
bacteria; eubacteria; microorganisms
RN **9025-75-6** (PROTEIN PHOSPHATASE)
56-45-1 (SERINE)
72-19-5 (THREONINE)
60-18-4 (TYROSINE)

L150 ANSWER 32 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:413789 BIOSIS
DN PREV199396079514
TI Comparison of conformations of cyclosporin A and macrolide FK506 fragments: Localization of putative binding sites with phosphatase **calcineurin**.
AU Denesyuk, Alexander I. (1); Korpela, Timo; Lundell, Juhani; Sara, Rolf; Zav'yalov, Vladimir P.
CS (1) Inst. Immunol., 142380 Lyubuchany, Moscow Region Russia
SO Biochemical and Biophysical Research Communications, (1993) Vol. 194, No. 1, pp. 280-286.
ISSN: 0006-291X.
DT Article
LA English
AB The **three-dimensional** structures of two immunosuppressants, cyclosporin A and macrolide FK506, were compared. The sites N-methylglycine3-N-methylleucine4 and valine5-N-methylleucine6 of cyclosporin A were found to be similar to each other (the root-mean-square value was 0.29 ANG for six reference points of the main chain) and also to the site C17-C22 of FK506 (the root-mean-square values were 0.33 ANG and 0.13 ANG , respectively). We suggest these fragments of cyclosporin A and FK506 make a major contribution to the interaction of the immunosuppressants with the phosphatase **calcineurin**.
CC Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical 10806
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids 13012
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - General; Methods *34502
BC Vertebrata - Unspecified *85150
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Pharmacology
IT Chemicals & Biochemicals
CYCLOSPORIN A; FK506
IT Miscellaneous Descriptors
IMMUNOLOGIC-DRUG; PHARMACODYNAMICS; T CELLS; T LYMPHOCYTE ACTIVATION
ORGN Super Taxa

Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia; Vertebrata - Unspecified: Vertebrata, Chordata, Animalia
ORGN Organism Name
human (Hominidae); Vertebrata (Vertebrata - Unspecified)
ORGN Organism Superterms
animals; chordates; humans; mammals; nonhuman vertebrates; primates; vertebrates
RN 59865-13-3 (CYCLOSPORIN A)
104987-11-3 (FK506)

L150 ANSWER 33 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:346736 BIOSIS
DN PREV199396043736
TI FK-506-binding protein: **Three-dimensional** structure of the complex with the antagonist L-685818.
AU Becker, Joseph W. (1); Rotonda, Jennifer; McKeever, Brian M.; Chan, H. Karen; Marcy, Alice I.; Wiederrecht, Greg; Hermes, Jeffery D.; Springer, James P.
CS (1) Merck Res. Lab., P.O. Box 2000 (R80M-203), Rahway, NJ 07065-0900 USA
SO Journal of Biological Chemistry, (1993) Vol. 268, No. 15, pp. 11335-11339. ISSN: 0021-9258.
DT Article
LA English
AB L-685,818 differs only slightly in structure from the immunosuppressive drug FK-506, and both compounds bind with comparable affinity to the 12-kDa FK-506-binding protein (FKBP12), the major intracellular receptor for the drug. Despite these similarities, L-685,818 is a potent antagonist of both the immunosuppressive and toxic effects of the drug. Here, we present a structural analysis of this problem. Although FK-506 and L-685,818 differ greatly in pharmacology, we have found that the **three-dimensional** structures of their complexes with FKBP12 are essentially identical. Approximately half of each ligand is in contact with the receptor protein, and half is exposed to solvent; the exposed region includes the two sites where the compounds differ. These results indicate that the profound differences in the pharmacology of these two compounds are not caused by any difference in their interaction with FKBP12. Rather, these effects arise because relatively minor changes in the exposed part of a bound ligand have a strong effect on how FKBP12-ligand complexes interact with **calcineurin**, their putative intracellular target. In addition, FK-506 complexes with FKBP12 proteins from several species all inhibit mammalian **calcineurin**. Analysis of the threedimensional structure of the complex with respect to residues conserved among these proteins suggests a small number of surface residues near the bound ligands that may play a critical role in interactions between the protein-drug complex and **calcineurin**.
CC Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Pharmacology - Immunological Processes and Allergy *22018
BC Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology
IT Chemicals & Biochemicals
L-685818
IT Miscellaneous Descriptors
ANTIGEN PRESENTATION; EAR SWELLING; IMMUNOSUPPRESSANT EFFECT; MAJOR HISTOCOMPATIBILITY COMPLEX CLASS II EXPRESSION; PROTEIN SYNTHESIS INHIBITION; TRICHOTHECENE MYCOTOXIN
ORGN Super Taxa
Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Hominidae (Hominidae)
ORGN Organism Superterms
animals; chordates; humans; mammals; primates; vertebrates
RN 143839-74-1 (L-685818)

L150 ANSWER 34 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:335933 BIOSIS
DN PREV199345030658
TI Identification of the **calcineurin** B-binding domain: A dimeric enzyme **structure** is required for immunophilin interactions and transcriptional activation in vivo.
AU Ueki, K.; Muramatsu, T.; Kincaid, R. L.
CS Immunol. Sect., NIAAA/NIH, Rockville, MD 20852 USA
SO FASEB Journal, (1993) Vol. 7, No. 7, pp. A1158.
Meeting Info.: **Joint Meeting of the American Society for Biochemistry and Molecular Biology and American Chemical Society Division of Biological Chemistry** San Diego, California, USA May 30-June 3, 1993
ISSN: 0892-6638.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Replication, Transcription, Translation *10300
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
BC Animalia - Unspecified *33000
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Genetics; Membranes (Cell Biology); Metabolism; Molecular Genetics (Biochemistry and Molecular Biophysics)
IT Chemicals & Biochemicals
CALCINEURIN
IT Miscellaneous Descriptors
ABSTRACT; MOLECULAR INTERACTION; REPORTER GENE RESPONSE
ORGN Super Taxa
Animalia - Unspecified: Animalia
ORGN Organism Name
animal (Animalia - Unspecified); Animalia (Animalia - Unspecified)
ORGN Organism Superterms
animals
RN **9025-75-6 (CALCINEURIN)**

L150 ANSWER 35 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:335921 BIOSIS
DN PREV199345030646
TI **Structure**-function relationship of protein phosphatase inhibitor-2.
AU Park, I.-K.; Depaoli-Roach, A. A.
CS Dep. Biochem. and Mol. Biol., Indiana Univ. Sch. Med., Indianapolis, IN 46202-5122 USA
SO FASEB Journal, (1993) Vol. 7, No. 7, pp. A1156.
Meeting Info.: **Joint Meeting of the American Society for Biochemistry and Molecular Biology and American Chemical Society Division of Biological Chemistry** San Diego, California, USA May 30-June 3, 1993
ISSN: 0892-6638.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508

Enzymes - Physiological Studies *10808
Metabolism - General Metabolism; Metabolic Pathways *13002
Metabolism - Proteins, Peptides and Amino Acids *13012
BC Animalia - Unspecified *33000
IT Major Concepts
Biochemistry and Molecular Biophysics; Cell Biology; Enzymology (Biochemistry and Molecular Biophysics); Membranes (Cell Biology); Metabolism; Methods and Techniques
IT Chemicals & Biochemicals
PROTEIN PHOSPHATASE
IT Miscellaneous Descriptors
ABSTRACT; ACTIVATION MECHANISM; C-TERMINAL MOLECULAR **STRUCTURE**; SYNERGISTIC PHOSPHORYLATION
ORGN Super Taxa
Animalia - Unspecified: Animalia
ORGN Organism Name
animal (Animalia - Unspecified); Animalia (Animalia - Unspecified)
ORGN Organism Superterms
animals
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 36 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:278487 BIOSIS
DN PREV199396008712
TI Improved **calcineurin** inhibition by yeast FKBP 12-drug complexes: **Crystallographic** and functional analysis.
AU Rotonda, Jennifer; Burbaum, Jonathan J.; Chan, H. Karen; Marcy, Alice I.; Becker, Joseph W. (1)
CS (1) Merck Res. Lab., P.O. Box 2000, Rahway, NJ 07065-0900 USA
SO Journal of Biological Chemistry, (1993) Vol. 268, No. 11, pp. 7607-7609. ISSN: 0021-9258.
DT Article
LA English
AB The protein phosphatase **calcineurin** is the putative target for the immunosuppressive drug FK-506. The enzyme is inhibited by the complex of the drug with its intracellular receptor, the 12-kDa FK-506-binding protein (FKBP12), and the strength of inhibition usually correlates strongly with immunosuppressive potency. We find, however, that the complex of yeast FKBP12 with L-685,818, a well characterized antagonist of FK-506 immunosuppression, is a potent inhibitor of **calcineurin**. The corresponding human complex does not inhibit the enzyme, and both human and yeast complexes with FK-506 do inhibit. To understand the structural basis of these findings, we have determined the **three -dimensional** structure of the complex of yeast FKBP12 with FK-506 by x-ray **crystallography**, and have found that the structure of the yeast complex is strikingly similar to its human homolog. These observations indicate that specific sequence elements in the yeast protein provide stronger binding interactions with a heterologous **calcineurin** than do the corresponding elements in the human protein, and suggest structural modifications that may improve the potency of this class of immunosuppressants.
CC Comparative Biochemistry, General *10010
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - General; Methods *34502
Pharmacognosy and Pharmaceutical Botany *54000
BC Fungi - Unspecified 15000
Hominidae *86215
IT Major Concepts
Biochemistry and Molecular Biophysics; Enzymology (Biochemistry and Molecular Biophysics); Immune System (Chemical Coordination and Homeostasis); Pharmacognosy (Pharmacology); Pharmacology
IT Chemicals & Biochemicals
CALCINEURIN

IT Miscellaneous Descriptors
FK-506 BINDING PROTEIN; IMMUNOSUPPRESSANT-DRUG; STRUCTURAL COMPARISON
ORGN Super Taxa
Fungi - Unspecified: Fungi, Plantae; Hominidae: Primates, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
fungi (Fungi - Unspecified); human (Hominidae)
ORGN Organism Superterms
animals; chordates; fungi; humans; mammals; microorganisms; nonvascular plants; plants; primates; vertebrates
RN **9025-75-6 (CALCINEURIN)**

L150 ANSWER 37 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:242154 BIOSIS
DN PREV199344115354
TI **Three-dimensional** solution **structure** of the cyclosporin A-cyclophilin complex by NMR.
AU Theriault, Yves; Logan, Timothy M.; Meadows, Robert P.; Yu, Liping; Olejniczak, Edward T.; Holzman, Thomas F.; Simmer, Robert L.; Fesik, Stephen W.
CS Pharm. Discovery Div., Abbott Lab., Abbott Park, IL 60064 USA
SO Journal of Cellular Biochemistry Supplement, (1993) Vol. 0, No. 17 PART C, pp. 285.
Meeting Info.: **Keystone Symposium on Frontiers of NMR in Molecular Biology III** Taos, New Mexico, USA March 8-14, 1993
ISSN: 0733-1959.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - Animal *03506
Biochemical Methods - Proteins, Peptides and Amino Acids *10054
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Endocrine System - General *17002
Pharmacology - Immunological Processes and Allergy *22018
Immunology and Immunochemistry - General; Methods *34502
BC Mammalia - Unspecified *85700
IT Major Concepts
Endocrine System (Chemical Coordination and Homeostasis); Enzymology (Biochemistry and Molecular Biophysics); Genetics; Immune System (Chemical Coordination and Homeostasis); Methods and Techniques; Pharmacology
IT Chemicals & Biochemicals
CYCLOSPORIN A
IT Miscellaneous Descriptors
ABSTRACT; CALCINEURIN INHIBITOR; IMMUNOSUPPRESSANT; INTERLEUKIN-2 GENE INHIBITOR; NMR
ORGN Super Taxa
Mammalia - Unspecified: Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Mammalia (Mammalia - Unspecified)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; vertebrates
RN 59865-13-3 (CYCLOSPORIN A)

L150 ANSWER 38 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:145324 BIOSIS
DN PREV199395078124
TI X-ray structure of a decameric cyclophilin-cyclosporin **crystal** complex.
AU Pflugl, Gaston; Kallen, Joerg; Schirmer, Tilman; Jansonius, Johan N.; Zurini, Mauro G. M.; Walkinshaw, Malcolm D. (1)
CS (1) Preclinical Res., Sandoz Pharma AG, 4002-Basel Switzerland
SO Nature (London), (1993) Vol. 361, No. 6407, pp. 91-94.

ISSN: 0028-0836.
DT Article
LA English
AB Human cyclophilin A (CypA), a ubiquitous intracellular protein of 165 amino acids, is the major receptor for the cyclic undecapeptide immunosuppressant drug cyclosporin A (CsA), which prevents allograft rejection after transplant surgery and is efficacious in the field of autoimmune diseases. CsA prevents T-cell proliferation by blocking the calcium-activated pathway leading to interleukin-2 transcription. Besides their ability to bind CsA, the cyclophilin isoforms-6-8 also have peptidyl-prolyl isomerase activity and enhance the rate of protein folding. The macrolide FK506 acts similarly to CsA and its cognate receptor FKBP also has peptidyl-prolyl isomerase activity. Inhibition of this enzymatic activity alone is not sufficient to achieve immunosuppression. A direct molecular interaction between the drug-immunophilin complex (CsA-CypA, or FK506-FKBP) and the phosphatase **calcineurin**, is responsible for modulating the T-cell receptor signal transduction pathway. Here we describe the **crystal** structure of a decameric CypA-CsA complex. The cystallographic asymmetric unit is composed of a pentamer of 1:1 cyclophilin-cyclosporin complexes of rather exact non-**crystallographic** fivefold symmetry. The 2.8 ANG electron density map is of high quality. The five independent cyclosporin molecules are clearly identifiable, providing an unambiguous picture of the detailed interactions between a peptide drug and its receptor. It broadly confirms the results of previous NMR, X-ray and modelling studies, but provides further important structural details which will be of use in the design of drugs that are analogues of CsA.
CC Radiation - Radiation and Isotope Techniques *06504
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Pharmacology - Immunological Processes and Allergy *22018
IT Major Concepts
Biochemistry and Molecular Biophysics; Pharmacology; Radiology (Medical Sciences)
IT Chemicals & Biochemicals
CYCLOSPORIN
IT Miscellaneous Descriptors
ANALYTICAL METHOD; IMMUNOSUPPRESSANT-DRUG; QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP
RN 59865-13-3Q (CYCLOSPORIN)
79217-60-0Q (CYCLOSPORIN)

L150 ANSWER 39 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:145323 BIOSIS
DN PREV199395078123
TI Solution structure of the cyclosporin A/cyclophilin complex by NMR.
AU Theriault, Yves; Logan, Timothy M.; Meadows, Robert; Yu, Liping; Olejniczak, Edward T.; Holzman, Thomas F.; Simmer, Robert L.; Fesik, Stephen W. (1)
CS (1) Pharmaceutical Discovery Div., Abbott Lab., Abbott Park, IL 60064 USA
SO Nature (London), (1993) Vol. 361, No. 6407, pp. 88-91.
ISSN: 0028-0836.
DT Article
LA English
AB Cyclosporin A, a cyclic undecapeptide, is a potent immunosuppressant that binds to peptidyl-prolyl cis-trans isomerase of 165 amino acids, cyclophilin. The cyclosporin A/cyclophilin complex inhibits the calcium- and calmodulin-dependent phosphatase, **calcineurin**, resulting in a failure to active genes encoding interleukin-2 and other lymphokines. The **three-dimensional** structures of uncomplexed cyclophilin, a tetrapeptide/cyclophilin complex, and cyclosporin A when bound to cyclophilin have been reported. However, the structure of the cyclosporin A/cyclophilin complex has not been determined. Here we present the solution structure of the cyclosporin A/cyclophilin complex obtained by heteronuclear **three-dimensional** NMR spectroscopy.

The structure, one of the largest determined by NMR, differs from proposed models of the complex and is analysed in terms of the binding interactions and structure/activity relationships for CsA analogues.

CC Radiation - Radiation and Isotope Techniques *06504
Biochemical Studies - General *10060
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - General Biophysical Techniques *10504
Biophysics - Molecular Properties and Macromolecules *10506
Pharmacology - Immunological Processes and Allergy *22018

IT Major Concepts
Biochemistry and Molecular Biophysics; Methods and Techniques; Pharmacology; Radiology (Medical Sciences)

IT Chemicals & Biochemicals
CYCLOSPORIN A

IT Miscellaneous Descriptors
ANALYTICAL METHOD; IMMUNOSUPPRESSANT-DRUG; QUANTITATIVE STRUCTURE-ACTIVITY RELATIONSHIP

RN 59865-13-3 (CYCLOSPORIN A)

L150 ANSWER 40 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1993:132589 BIOSIS
DN PREV199344063589
TI **Structure** and physiological significance of a rat testis specific **calcineurin** beta isoform.
AU Matsui, H.; Nishio, H.; Moia, L. J. M. P.; Tokuda, M.; Itano, T.; Miyamoto, K.; Hatase, O.
CS Dep. Physiol., Kagawa Med. Sch., Ikenobe, Miki, Kagawa 761-07 Japan
SO Japanese Journal of Physiology, (1992) Vol. 42, No. SUPPL., pp. S37.
Meeting Info.: **69th Annual Meeting of the Physiological Society of Japan** Akita, Japan April 2-4, 1992
ISSN: 0021-521X.
DT **Conference**
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules 10506
Biophysics - Membrane Phenomena *10508
Reproductive System - Physiology and Biochemistry *16504
Developmental Biology - Embryology - Morphogenesis, General *25508
BC Muridae *86375
IT Major Concepts
Cell Biology; Development; Membranes (Cell Biology); Reproductive System (Reproduction)
IT Miscellaneous Descriptors
ABSTRACT; CALMODULIN BINDING PROTEIN; SPERMATOGENESIS
ORGN Super Taxa
Muridae: Rodentia, Mammalia, Vertebrata, Chordata, Animalia
ORGN Organism Name
Muridae (Muridae)
ORGN Organism Superterms
animals; chordates; mammals; nonhuman vertebrates; nonhuman mammals; rodents; vertebrates

L150 ANSWER 41 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1992:357516 BIOSIS
DN BR43:35666
TI THE SOMATOSTATIN RECEPTOR IN THE GI TRACT.
AU LEWIN M J M
CS GI RES. UNIT, INSERM U.10, BICHAT HOSP., 75018 PARIS, FR.
SO HOFFMAN, J. F. (ED.). ANNUAL REVIEW OF PHYSIOLOGY, VOL. 54. XVII+965P. ANNUAL REVIEWS INC.: PALO ALTO, CALIFORNIA, USA. ILLUS. (1992) 0 (0), 455-468.
CODEN: ARPHAD. ISSN: 0066-4278. ISBN: 0-8243-0353-7.
FS BR; OLD

LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal 02506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Physiological Studies *10808
Digestive System - Physiology and Biochemistry *14004
Endocrine System - Neuroendocrinology *17020
Nervous System - Physiology and Biochemistry *20504
Neoplasms and Neoplastic Agents - Biochemistry *24006
BC Canidae 85765
Hominidae 86215
Muridae 86375
IT Miscellaneous Descriptors
RAT DOG HUMAN CALCIUM ADENYLATE CYCLASE G PROTEIN **PHOSPHOPROTEIN PHOSPHATASE** TUMOR GASTROINTESTINAL TRACT MOLECULAR **STRUCTURE**
RN 7440-70-2 (CALCIUM)
9012-42-4 (ADENYLATE CYCLASE)
9025-75-6 (PHOSPHOPROTEIN PHOSPHATASE)
38916-34-6Q, 51110-01-1Q (SOMATOSTATIN)

L150 ANSWER 42 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1991:310018 BIOSIS
DN BR41:18608
TI INDUCTION OF CONTRACTILE RING-LIKE **STRUCTURE** BY CALYCULIN A IN SEA URCHIN EGGS.
AU TOSUJI H; MABUCHI I; MIYAJI K; KATO Y; FUSETANI N; NAKAZAWA T
CS DEP. BIOL., FAC. SCI., TOHO UNIV., FUNABASHI, JPN.
SO SIXTY-FIRST ANNUAL **MEETING** OF THE ZOOLOGICAL SOCIETY OF JAPAN, NIIGATA, JAPAN, OCTOBER 3-5, 1990. ZOOL SCI (TOKYO). (1990) 7 (6), 1098.
CODEN: ZOSCEX. ISSN: 0289-0003.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies 10808
Anatomy and Histology, General and Comparative - Microscopic and Ultramicroscopic Anatomy *11108
Reproductive System - Anatomy 16502
Reproductive System - Physiology and Biochemistry *16504
Invertebrata, Comparative and Experimental Morphology, Physiology and Pathology - Porifera 64006
Invertebrata, Comparative and Experimental Morphology, Physiology and Pathology - Echinodermata *64048
BC Porifera 39000
Echinoidea 83300
IT Miscellaneous Descriptors
ABSTRACT DISCODERMIA-CALYX PROTEIN PHOSPHATASE CELL MICROTUBULE ULTRASTRUCTURE
RN **9025-75-6** (PROTEIN PHOSPHATASE)
101932-71-2 (CALYCULIN A)

L150 ANSWER 43 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1991:286556 BIOSIS
DN BR41:6976
TI CHEMICAL MODIFICATION OF A CALCIUM-SENSITIVE ALLOSTERIC SITE ON **CALCINEURIN**.
AU PLANK M B; KING M M
CS DEP. CHEM. AND OHIO STATE BIOCHEM. PROGRAM, THE OHIO STATE UNIV.,

COLUMBUS, OH 43210.
SO 75TH ANNUAL **MEETING** OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, ATLANTA, GEORGIA, USA, APRIL 21-25, 1991. FASEB (FED AM SOC EXP BIOL) J. (1991) 5 (4), A831.
CODEN: FAJOEC. ISSN: 0892-6638.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
BC Vertebrata - Unspecified 85150
IT Miscellaneous Descriptors
ABSTRACT STRUCTURE FUNCTION MECHANISM
RN 7440-70-2 (CALCIUM)

L150 ANSWER 44 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1990:460345 BIOSIS
DN BR39:95706
TI **STRUCTURE** AND EXPRESSION OF THE ALPHA AND BETA GENES ENCODING THE CATALYTIC SUBUNIT OF PROTEIN PHOSPHATASE 2A.
AU KHEW-GOODALL Y; MAYER R; MAURER F; STONE S; HEMMINGS B A
CS FRIEDRICH MIESCHER-INST., P.O. BOX 2543, CH-4002 BASEL, SWITZ.
SO NISHIZUKA, Y., M. ENDO AND C. TANAKA (ED.). ADVANCES IN SECOND MESSENGER AND PHOSPHOPROTEIN RESEARCH, VOL. 24. THE BIOLOGY AND MEDICINE OF SIGNAL TRANSDUCTION; 7TH INTERNATIONAL **CONFERENCE** ON CYCLIC NUCLEOTIDES, CALCIUM AND PROTEIN PHOSPHORYLATION, KOBE, JAPAN, OCTOBER 8-13, 1989. XXXIII+750P. RAVEN PRESS: NEW YORK, NEW YORK, USA. ILLUS. (1990) 0 (0), 642.
CODEN: ASMRE5. ISBN: 0-88167-670-5.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Chemical and Physical *10806
BC Hominidae 86215
IT Miscellaneous Descriptors
ABSTRACT HUMAN SIGNAL TRANSDUCTION
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 45 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1990:460012 BIOSIS
DN BR39:95373
TI MULTIPLE FORMS OF **CALCINEURIN** A BRAIN ISOZYME OF THE CALMODULIN-STIMULATED PROTEIN PHOSPHATASE.
AU GUERINI D; HUBBARD M J; KRINKS M H; KLEE C B
CS LAB. BIOCHEM., NATL. CANCER INST., NATL. INST. HEALTH, BETHESDA, MD. 20892, USA.
SO NISHIZUKA, Y., M. ENDO AND C. TANAKA (ED.). ADVANCES IN SECOND MESSENGER AND PHOSPHOPROTEIN RESEARCH, VOL. 24. THE BIOLOGY AND MEDICINE OF SIGNAL TRANSDUCTION; 7TH INTERNATIONAL **CONFERENCE** ON CYCLIC NUCLEOTIDES, CALCIUM AND PROTEIN PHOSPHORYLATION, KOBE, JAPAN, OCTOBER 8-13, 1989. XXXIII+750P. RAVEN PRESS: NEW YORK, NEW YORK, USA. ILLUS. (1990) 0 (0), 242-247.
CODEN: ASMRE5. ISBN: 0-88167-670-5.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of**

Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Nervous System - Physiology and Biochemistry *20504
BC Mammalia - Unspecified 85700
IT Miscellaneous Descriptors
REVIEW DOMAIN **STRUCTURE** FUNCTION COMPLEMENTARY DNA SIGNAL TRANSDUCTION MOLECULAR SEQUENCE DATA AMINO ACID SEQUENCE
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 46 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1990:366508 BIOSIS
DN BR39:50984
TI **STRUCTURE** AND REGULATION OF **CALCINEURIN** A CALMODULIN-STIMULATED PROTEIN PHOSPHATASE.
AU KLEE C B; GUERINI D
CS LAB. BIOCHEM., NATL. CANCER INST., NATL. INST. HEALTH, BETHESDA, MD. 20892.
SO JOINT **MEETING** OF THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, AND THE AMERICAN ASSOCIATION OF IMMUNOLOGISTS, NEW ORLEANS, LOUISIANA, USA, JUNE 4-7, 1990. FASEB (FED AM SOC EXP BIOL) J. (1990) 4 (7), A2172.
CODEN: FAJOEC. ISSN: 0892-6638.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - Animal *03506
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Enzymes - Chemical and Physical *10806
BC Diptera 75314
Bovidae 85715
Hominidae 86215
IT Miscellaneous Descriptors
ABSTRACT HUMAN COW DROSOPHILA-MELANOGASTER AMINO ACID SEQUENCING COMPLEMENTARY DNA CLONES
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 47 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1990:274630 BIOSIS
DN BR39:6476
TI THE ALPHA AND BETA PROTEIN PHOSPHATASE 2A CATALYTIC SUBUNIT GENES SIMILAR **STRUCTURE** BUT DIFFERENT PROMOTERS.
AU MAYER R E; KHEW-GOODALL Y; STONE S R; HEMMINGS B A
CS FRIEDRICH MIESCHER-INST., CH-4002 BASEL.
SO 22ND ANNUAL **MEETING** OF THE SWISS SOCIETIES FOR EXPERIMENTAL BIOLOGY (USGEB/USSBE), ZUERICH, SWITZERLAND, MARCH 15-16, 1990. EXPERIENTIA (BASEL). (1990) 46 (ABSTR), A27.
CODEN: EXPEAM. ISSN: 0014-4754.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Evolution *01500
Genetics and Cytogenetics - Human *03508
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
BC Hominidae 86215

IT Miscellaneous Descriptors
ABSTRACT HUMAN GENE DUPLICATION PROMOTER DNA MOLECULAR SEQUENCE DATA MOLECULAR EVOLUTION
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 48 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1989:489161 BIOSIS
DN BA88:115698
TI EFFECTS OF MODIFYING INDIVIDUAL AMINO OR CARBOXYL GROUPS ON THE AFFINITY OF CALMODULIN FOR **CALCINEURIN**.
AU CHIN D; BREW K
CS DEP. BIOCHEM. MOL. BIOL. R-629 , UNIV. MIAMI SCH. MED., P.O. BOX 016129, MIAMI, FLA. 33101.
SO J BIOL CHEM, (1989) 264 (26), 15367-15375.
CODEN: JBCHA3. ISSN: 0021-9258.
FS BA; OLD
LA English
AB The effects of modifying individual lysyl, aspartyl, or glutamyl residues in calmodulin on its ability to bind to the neural phosphatase **calcineurin** have been investigated using a competitive binding method termed "label selection." Samples of calmodulin were radiochemically labeled at a low level (0.03-0.6 group/molecule) by acetylation of amino groups or coupling carboxyl groups with ethanolamine to produce preparations containing predominantly single-site modified and unmodified molecules. These preparations were incubated in a 5-10-fold molar excess with bovine **calcineurin** under conditions appropriate for complex formation. The bound population was isolated, and the level of modification of each reactive residue was compared with the level in the corresponding group in the initial unselected preparations to determine if molecules modified at specific sites had been selected for or against during the competition for complex formation. Significant selection was observed against molecules modified at Lys21, Asp64, Glu67, Lys75, Glu84, Glu114, Asp118, or Lys148, whereas modification of Glu83 increased binding. The modification of other groups, including components of the four Ca2+-binding sites, had no effect on the interaction. Glu687, a Ca2+-liganding residue in ca2+-binding site II that may regulate the orientation of this site in relation to the central helix, had the strongest influence on complex formation. Most of the residues identified form a nearly linear array in the **three-dimensional** structure of calmodulin and indicate the location of an extended surface for interaction with clacineurin and other enzymes.
CC Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Metabolism - Proteins, Peptides and Amino Acids *13012
IT Miscellaneous Descriptors
THREE DIMENSIONAL STRUCTURE LABEL SELECTION COMPETITIVE BINDING METHOD LYSYL RESIDUE MODIFICATION ASPARTYL GROUP GLUTAMYL GROUP

L150 ANSWER 49 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1989:454380 BIOSIS
DN BA88:102652
TI THE DEPHOSPHORYLATION OF LENS ALPHA **CRYSTALLIN** A CHAIN.
AU CHIESA R; SPECTOR A
CS BIOCHEM. AND MOL. BIOL. LAB., DEP. OPHTHALMOL., COLL. PHYSICIANS AND SURG. COLUMBIA UNIV., NEW YORK, N. Y. 10032.
SO BIOCHEM BIOPHYS RES COMMUN, (1989) 162 (3), 1494-1501.
CODEN: BBRCA9. ISSN: 0006-291X.
FS BA; OLD
LA English
AB The present communication reports the presence of a **phosphoprotein phosphatase** activity in bovine lens preparations which dephosphorylates .alpha.Ap, the phosphorylated form of .alpha.A, one of the .alpha.-**crystallin** polypeptides, in a Ca2+/calmodulin dependent manner. The activity was found in soluble preparations from

epithelial cells but it could not be detected in similar preparations from fiber cells. A 60,000 Mr calmodulin binding polypeptide and a 15,000 Mr polypeptide found in the epithelial cell preparations comigrated in SDS-PAGE with the A and B subunits of bovine brain **calcineurin** (**phosphoprotein phosphatase** 2B) respectively. The 15,000 Mr was specifically recognized by an anti-bovine brain **calcineurin** antiserum. Bovine brain **calcineurin** was as effective in dephosphorylating .alpha.Ap as the lens preparations. Thus, it is likely that the activity present in the lens is related to this enzyme. The results indicate that the lens specific polypeptide .alpha.A may be subject to metabolic control through phosphorylation and dephosphorylation pathways regulated by cAMP and calcium, respectively. Changes in the activities of these pathways appear to occur during differentiation of the lens epithelial cell and may be related to gene regulation during the differentiation process.

CC Cytology and Cytochemistry - Animal *02506
Genetics and Cytogenetics - Animal 03506
Comparative Biochemistry, General 10010
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - General and Comparative Studies; Coenzymes 10802
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Metabolism - Minerals *13010
Metabolism - Proteins, Peptides and Amino Acids *13012
Sense Organs, Associated Structures and Functions - Physiology and Biochemistry *20004
Nervous System - Physiology and Biochemistry 20504
Developmental Biology - Embryology - Morphogenesis, General 25508

BC Bovidae 85715

IT Miscellaneous Descriptors
BOVINE EPITHELIAL CELL DIFFERENTIATION CALCIUM CALMODULIN DEPENDENT **PHOSPHOPROTEIN PHOSPHATASE CALCINEURIN** GENE REGULATION

RN 50-14-6 (**CRYSTALLIN** A)
7440-70-2 (CALCIUM)
9025-75-6 (**PHOSPHOPROTEIN PHOSPHATASE**)

L150 ANSWER 50 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1989:193774 BIOSIS
DN BR36:94223
TI A SMALL INHIBITION PEPTIDE CAN BE REMOVED FROM THE CATALYTIC SUBUNIT OF ERYTHROCYTE **PHOSPHOPROTEIN PHOSPHATASE**.
AU **KIM J S**; WESTHEAD E W
CS BIOCHEM. DEP., UNIV. MASS., AMHERST, MASS. 01003.
SO JOINT MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY AND THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND MOLECULAR BIOLOGY, SAN FRANCISCO, CALIFORNIA, USA, JANUARY 29-FEBRUARY 2, 1989. J CELL BIOL. (1988) 107 (6 PART 3), 840A.
CODEN: JCLBA3. ISSN: 0021-9525.
DT Conference
FS BR; OLD
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Cytology and Cytochemistry - Human *02508
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Chemical and Physical *10806
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
BC Hominidae 86215
IT Miscellaneous Descriptors
ABSTRACT HUMAN
RN **9025-75-6** (**PHOSPHOPROTEIN PHOSPHATASE**)

L150 ANSWER 51 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1989:90222 BIOSIS
DN BA87:44358
TI EFFECTS OF INTERACTION WITH **CALCINEURIN** ON THE REACTIVITIES OF CALMODULIN LYSINES.
AU WEI Q; JACKSON A E; PERVAIZ S; CARRAWAY K I III; LEE E Y C; PUETT D; BREW K
CS DEP. BIOCHEM. MOL. BIOL., UNIV. MIAMI SCH. MED., P.O. BOX 016129, MIAMI, FLA. 33101.
SO J BIOL CHEM, (1988) 263 (36), 19541-19544.
CODEN: JBCHA3. ISSN: 0021-9258.
FS BA; OLD
LA English
AB Calmodulin was trace labeled by acetylation with [3H]acetic anhydride in the presence and absence of a 30% molar excess of the phosphatase **calcineurin**; phenylalanine was included in the reaction mixtures as an internal standard. The level of 3H acetylation of each of the 7 lysines was determined and corrected for differences arising from reaction conditions using the labeling of the internal standard, following procedures that are closely similar to those used in a previous study of the interaction of calmodulin with myosin light chain kinase (Jackson, A. E., Carraway, K. L., III, Puett, D., and Brew, K. (1986) J. Biol. Chem. 261, 12226-12232). The interaction with calcineurin **was** found to produce a 10-fold reduction in the acetylation of lysine 75, with lesser but significant effects on lysines 21 and 148. A small but reproducible perturbation of lysine 77 was also observed. The results are similar to those that are produced by the interaction with myosin light chain kinase. However, when they are compared with two recent reports between which there are major discrepancies (Manalan, A. S., and Klee, C. B. (1987) Biochemistry 26, 1382-1390; Winkler, M. A., Fried, V. A., Merat, D. L., and Cheung, W. Y. (1987) J. Biol. Chem. 262, 15466-15471), our results are in good agreement with those obtained in the former study. From the location of the perturbed groups in the three-dimensional structure **of calmodulin**, it appears that the interaction site on calmodulin for calcineurin, as well **as** for myosin light chain kinase, is very extended and may include hybrophobic pockets at homologous sites near the carboxyl-terminal ends of the two halves of the molecule.
CC Biochemical Methods - Proteins, Peptides and Amino Acids 10054
Biochemical Methods - Minerals 10059
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals *10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806
IT Miscellaneous Descriptors
MYOSIN LIGHT CHAIN KINASE CALCIUM-BINDING PROTEIN
RN 56-87-1D (LYSINES)

L150 ANSWER 52 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1988:451352 BIOSIS
DN BR35:92232
TI THE DOMAIN **STRUCTURE** OF **CALCINEURIN**.
AU KLEE C B; KRINKS M H; HUBBARD M J
CS LAB. BIOCHEM., NATL. CANCER INST., NATL. INST. HEALTH, BETHESDA, MD.
SO NORMAN, A. W., T. C. VANAMAN AND A. R. MEANS (ED.). CALCIUM-BINDING PROTEINS IN HEALTH AND DISEASE; FIFTH INTERNATIONAL **SYMPOSIUM**, PACIFIC GROVE, CALIFORNIA, USA, NOVEMBER 30-DECEMBER 5, 1986. XIX+629P. ACADEMIC PRESS, INC.: SAN DIEGO, CALIFORNIA, USA; LONDON, ENGLAND, UK. ILLUS. (1987) 0 (0), 481-490.
ISBN: 0-12-521040-X.
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical *10806

Enzymes - Physiological Studies *10808
Muscle - Physiology and Biochemistry *17504
Nervous System - Physiology and Biochemistry *20504
IT Miscellaneous Descriptors
CALMODULIN-STIMULATED PROTEIN PHOSPHATASE BRAIN EXTRACTS MYOSIN LIGHT CHAIN KINASE
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 53 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1988:451311 BIOSIS
DN BR35:92191
TI USE OF GENETICALLY ENGINEERED CALMODULINS AS **STRUCTURE**-FUNCTION PROBES.
AU PUTKEY J A; MEANS A R
CS DEP. BIOCHEM. MOL. BIOL., UNIV. TEX. MED. SCH., HOUSTON, TEX.
SO NORMAN, A. W., T. C. VANAMAN AND A. R. MEANS (ED.). CALCIUM-BINDING PROTEINS IN HEALTH AND DISEASE; FIFTH INTERNATIONAL **SYMPOSIUM**, PACIFIC GROVE, CALIFORNIA, USA, NOVEMBER 30-DECEMBER 5, 1986. XIX+629P. ACADEMIC PRESS, INC.: SAN DIEGO, CALIFORNIA, USA; LONDON, ENGLAND, UK. ILLUS. (1987) 0 (0), 267-275.
ISBN: 0-12-521040-X.
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Genetics and Cytogenetics - Animal *03506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals 10069
Enzymes - Physiological Studies *10808
BC Galliformes 85536
IT Miscellaneous Descriptors
CHICKEN SITE-DIRECTED MUTAGENESIS MYOSIN LIGHT CHAIN KINASE PHOSPHODIESTERASE **CALCINEURIN**
RN 9025-82-5 (PHOSPHODIESTERASE)

L150 ANSWER 54 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1988:435734 BIOSIS
DN BA86:87832
TI FUNCTIONAL SIGNIFICANCE OF THE CENTRAL HELIX IN CALMODULIN.
AU PUTKEY J A; ONO T; VANBERKUM M F A; MEANS A R
CS DEP. CELL BIOL., BAYLOR COLL. MED., 1 BAYLOR PL., HOUSTON, TEXAS 77030.
SO J BIOL CHEM, (1988) 263 (23), 11242-11249.
CODEN: JBCHA3. ISSN: 0021-9258.
FS BA; OLD
LA English
AB The 3-.ANG. **crystal** structure of calmodulin indicates that it has a polarized tertiary arrangement in which calcium binding domains I and II are separated from domains III and IV by a long central helix consisting of residues 65-92. To investigate the functional significance of the central helix, mutated calmodilins were engineered with alterations in this region. Using oligonucleotide-primed site-directed mutagenesis, Thr-79 was converted to Pro-79 to generate CaMPM. CaMPM was further mutated by insertion of Pro-Ser-Thr-Asp between Asp-78 and Pro-79 to yield CaMIM. Calmodulin, CaMPM, and CaMIM were indistinguisable in their ability to activate **calcineurin** and Ca2+-ATPase. All mutated calmodulins would also maximally activate cGMP-phosphodiesterase and myosin light chain kinase, however, the concentrations of CaMPM and CaMIM necessary for half-maximal activation (Kact) were 2- and 9-fold greater, respectively, than CaM23. Conversion of the 2 Pro residues in CaMIM to amino acids that predict retention of helical secondary structure did not restore normal calmodulin activity. To investigate the nature of the interaction between mutated calmodulins and target enzymes, synthetic peptides modeled after the calmodulin binding region of smooth and skeletal muscle myosin light chain kinase were prepared and used as inhibitors of calmodulin-dependent cGMP-phosphodiesteras. The data suggest that the different kinetics of activation of myosin light chain kinase by CaM23 and CaMIM are not due to

differences in the ability of the activators to bind to the calmodulin binding site of this enzyme. These observations are consistent with a model in which the length but not composition of the central helix is more important for the activation of certain enzymes. The data also support the hypothesis that calmodulin contains multiple sites for protein-protein interaction that are differentially recognized by its multiple target proteins.

CC Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Chemical and Physical 10806
Metabolism - Minerals *13010

IT Miscellaneous Descriptors
MOLECULAR STRUCTURE CALCIUM BINDING ENZYME ACTIVATION

L150 ANSWER 55 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1988:66121 BIOSIS
DN BR34:32817
TI **PHOSPHOPROTEIN PHOSPHATASES** IN HUMAN ERYTHROCYTES.
AU **KIM J S**; WESTHEAD E W
CS UNIV. MASS., AMHERST, MASS. 01003.
SO TWENTY-SEVENTH ANNUAL MEETING OF THE AMERICAN SOCIETY FOR CELL BIOLOGY, ST. LOUIS, MISSOURI, USA, NOVEMBER 16-20, 1987. J CELL BIOL. (1987) 105 (4 PART 2), 19A.
CODEN: JCLBA3. ISSN: 0021-9525.
DT Conference
FS BR; OLD
LA English
CC General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Blood, Blood-Forming Organs and Body Fluids - Blood Cell Studies *15004
Muscle - Physiology and Biochemistry 17504
BC Hominidae 86215
IT Miscellaneous Descriptors
ABSTRACT RABBIT MUSCLE PROTEIN INHIBITOR CYCLIC AMP DEPENDENT PROTEIN KINASE
RN 60-92-4 (CYCLIC AMP)
9025-75-6D (**PHOSPHOPROTEIN PHOSPHATASES**)
9026-43-1 (PROTEIN KINASE)

L150 ANSWER 56 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1986:334700 BIOSIS
DN BR31:49282
TI **STRUCTURE** AND REGULATION OF PROTEIN PHOSPHATASE INHIBITOR 2 FROM RABBIT SKELETAL MUSCLE.
AU HOLMES C F B; COHEN P
CS DEP. BIOCHEM., UNIV. DUNDEE, SCOTLAND, DD1 4HN.
SO 76TH ANNUAL **MEETING** OF THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, WASHINGTON, D.C., USA, JUNE 8-12, 1986. FED PROC. (1986) 45 (6), 1802.
CODEN: FEPRA7. ISSN: 0014-9446.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids *10064
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - General and Comparative Studies; Coenzymes *10802
Muscle - Physiology and Biochemistry *17504
BC Leporidae 86040
IT Miscelláneous Descriptors

ABSTRACT
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 57 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1985:214990 BIOSIS
DN BR29:104986
TI PROTEIN KINASES IN THE BRAIN.
AU NAIRN A C; HEMMINGS H C JR; GREENGARD P
CS LAB. MOLECULAR CELLULAR NEUROSCI., ROCKEFELLER UNIV., 1230 YORK AVE., NEW YORK, N.Y. 10021.
SO RICHARDSON, C. C. (ED.). ANNUAL REVIEW OF BIOCHEMISTRY, VOL. 54. XII+1335P. ANNUAL REVIEWS INC.: PALO ALTO, CALIF., USA. ILLUS. (1985) 0 (0), 931-976.
CODEN: ARBOAW. ISSN: 0066-4154. ISBN: 0-8243-0854-9.
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines *10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals *10069
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Nervous System - Physiology and Biochemistry *20504
IT Miscellaneous Descriptors
REVIEW CYCLIC AMP CYCLIC GMP CALCIUM **STRUCTURE** DISTRIBUTION SUBSTRATE PROTEINS **PHOSPHOPROTEIN PHOSPHATASES**
RN 60-92-4 (CYCLIC AMP)
7440-70-2 (CALCIUM)
7665-99-8 (CYCLIC GMP)
9025-75-6D (**PHOSPHOPROTEIN PHOSPHATASES**)
9026-43-1D (PROTEIN KINASES)

L150 ANSWER 58 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1985:125149 BIOSIS
DN BR29:15145
TI **CALCINEURIN** A BRAIN-SPECIFIC ISOZYME OF PROTEIN PHOSPHATASE 2 B.
AU KRINKS M H; MANALAN A S; KLEE C B
CS LAB. BIOCHEM., NCI, NIH, BETHESDA, MD. 20205.
SO 69TH ANNUAL **MEETING** OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, ANAHEIM, CALIF., USA, APR. 21-26, 1985. FED PROC. (1985) 44 (3), 707.
CODEN: FEPRA7. ISSN: 0014-9446.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Comparative Biochemistry, General 10010
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - General and Comparative Studies; Coenzymes 10802
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Nervous System - Physiology and Biochemistry *20504
Developmental Biology - Embryology - General and Descriptive 25502
Immunology and Immunochemistry - General; Methods 34502
Invertebrata, Comparative and Experimental Morphology, Physiology and Pathology - Insecta - Physiology 64076
BC Diptera 75314
Bovidae 85715
Leporidae 86040
Muridae 86375
IT Miscellaneous Descriptors
ABSTRACT BOVINE RAT RABBIT DROSOPHILA EMBRYO CALMODULIN

CALCIUM IMMUNOLOGIC CROSS-REACTIVITY SUBUNIT **STRUCTURE**
RN 7440-70-2 (CALCIUM)
9025-75-6 (PROTEIN PHOSPHATASE)

L150 ANSWER 59 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1985:125148 BIOSIS
DN BR29:15144
TI **CALCINEURIN**-PHOSPHATASE NICKEL-BINDING PROPERTIES.
AU PALLEN C J; WANG J H
SO 69TH ANNUAL **MEETING** OF THE FEDERATION OF AMERICAN SOCIETIES FOR EXPERIMENTAL BIOLOGY, ANAHEIM, CALIF., USA, APR. 21-26, 1985. FED PROC. (1985) 44 (3), 707.
CODEN: FEPRA7. ISSN: 0014-9446.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Enzymes - Chemical and Physical *10806
IT Miscellaneous Descriptors
ABSTRACT CALCIUM CALMODULIN SUBUNIT **STRUCTURE**
RN 7440-70-2 (CALCIUM)

L150 ANSWER 60 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1985:124146 BIOSIS
DN BR29:14142
TI REVISED MODEL FOR THE NUCLEOSIDE TRIPHOSPHATASE-MEDIATED POLYADENYLATED MESSENGER RNA EFFLUX FROM NUCLEUS TO CYTOPLASM.
AU MUELLER W E G; SCHROEDER H C; BACHMANN M; BERND A
CS UNIV. 6500 MAINZ, WEST GERMANY.
SO **SYMPOSIUM** ON THE NUCLEAR ENVELOPE STRUCTURE AND RNA MATURATION HELD AT THE 14TH ANNUAL **MEETING** OF THE UCLA (UNIVERSITY OF CALIFORNIA-LOS ANGELES) **SYMPOSIA** ON MOLECULAR AND CELLULAR BIOLOGY, JAN 12-19, 1985. J CELL BIOCHEM. (1985) 0 (9 PART A), 22.
CODEN: JCBSD7.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Cytology and Cytochemistry - Animal *02506
Biochemical Studies - Nucleic Acids, Purines and Pyrimidines 10062
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules *10506
Biophysics - Membrane Phenomena *10508
Enzymes - Physiological Studies *10808
Digestive System - General; Methods 14001
Reproductive System - General; Methods 16501
BC Galliformes 85536
IT Miscellaneous Descriptors
ABSTRACT QUAIL LIVER OVIDUCT PROTEIN KINASE **PHOSPHOPROTEIN PHOSPHATASE** NUCLEAR ENVELOPE CARRIER **STRUCTURE**
RN **9025-75-6** (**PHOSPHOPROTEIN PHOSPHATASE**)
9026-43-1 (PROTEIN KINASE)
9075-51-8 (NUCLEOSIDE TRIPHOSPHATASE)

L150 ANSWER 61 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1983:122066 BIOSIS
DN BR25:47066
TI MONO CLONAL ANTIBODIES TO RABBIT SKELETAL MUSCLE PROTEIN PHOSPHATASE C.
AU SPETH M; ALEJANDRO R; LEE E Y C
CS UNIV. MIAMI, FLA. 33136.
SO 74TH ANNUAL **MEETING** OF THE AMERICAN SOCIETY OF BIOLOGICAL

CHEMISTS, SAN FRANCISCO, CALIF., USA, JUNE 5-9, 1983. FED PROC. (1983) 42 (7), **ABSTRACT** 1592.
CODEN: FEPRA7. ISSN: 0014-9446.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Carbohydrates 10068
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Physiological Studies *10808
Blood, Blood-Forming Organs and Body Fluids - Lymphatic Tissue and Reticuloendothelial System *15008
Muscle - Physiology and Biochemistry *17504
Immunology and Immunochemistry - General; Methods *34502
BC Leporidae 86040
IT Miscellaneous Descriptors
ABSTRACT SPLEEN CELL **STRUCTURE**
RN **9025-75-6** (PROTEIN PHOSPHATASE)

L150 ANSWER 62 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1983:122039 BIOSIS
DN BR25:47039
TI PROTEIN PHOSPHATASE 2B A CALCIUM ION AND CALMODULIN DEPENDENT ENZYME.
AU COHEN P; AITKEN A; KLEE C B; TONKS N; STEWART A A
CS DEP. OF BIOCHEM., UNIV. OF DUNDEE.
SO 74TH ANNUAL **MEETING** OF THE AMERICAN SOCIETY OF BIOLOGICAL CHEMISTS, SAN FRANCISCO, CALIF., USA, JUNE 5-9, 1983. FED PROC. (1983) 42 (7), **ABSTRACT** 255.
CODEN: FEPRA7. ISSN: 0014-9446.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biochemical Studies - Minerals 10069
Biophysics - Molecular Properties and Macromolecules *10506
Enzymes - Physiological Studies *10808
Muscle - Physiology and Biochemistry *17504
IT Miscellaneous Descriptors
ABSTRACT PRIMARY **STRUCTURE**
RN **9025-75-6** (PROTEIN PHOSPHATASE)
14127-61-8 (CALCIUM ION)

L150 ANSWER 63 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1982:107017 BIOSIS
DN BR23:37009
TI REGULATION OF PROTEIN PHOSPHATASE 1 VIA GLYCOGEN PHOSPHORYLASE.
AU MADSEN N B; FLETTERICK R J; KASVINSKY P J
CS DEP. BIOCHEM., UNIV. ALBERTA, EDMONTON, ALBERTA, CAN. T6G 2H7.
SO ROSEN, O. M. AND E. G. KREBS (ED.). COLD SPRING HARBOR **CONFERENCE** ON CELL PROLIFERATION, VOL. 8. PROTEIN PHOSPHORYLATION, PART A AND B. XXIII+711P.(PART A); XV+709P.(PART B) COLD SPRING HARBOR LABORATORY: COLD SPRING HARBOR, N.Y., USA. ILLUS. (1981) 0 (0), P483-496.
CODEN: CSHCAL. ISSN: 0097-5230. ISBN: 0-87969-140-9.
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Enzymes - Chemical and Physical *10806
Enzymes - Physiological Studies *10808
Digestive System - Physiology and Biochemistry 14004
BC Muridae 86375

IT Miscellaneous Descriptors
RAT LIVER **CRYSTAL STRUCTURE**
RN **9025-75-6** (PROTEIN PHOSPHATASE)
9035-74-9 (GLYCOGEN PHOSPHORYLASE)

L150 ANSWER 64 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1982:60520 BIOSIS
DN BR22:60520
TI SUBUNIT **STRUCTURE** AND REGULATION OF A PIG HEART PHOSPHO PROTEIN PHOSPHATASE.
AU TAKEDA M; IMAZU M; IMAOKA T; USUI H; KINOHARA N
CS DEP. BIOCHEM., HIROSHIMA UNIV. SCH. MED., HIROSHIMA, JPN.
SO DUMONT, J. E., P. GREENGARD AND G. A. ROBISON (ED.). ADVANCES IN CYCLIC NUCLEOTIDE RESEARCH, VOL. 14. 4TH INTERNATIONAL **CONFERENCE**, BRUSSELS, BELGIUM, JULY 22-26, 1980. XXXI+724P. RAVEN PRESS: NEW YORK, N.Y., USA. ILLUS. (1981) 0 (0), P673.
CODEN: ACNRCW. ISSN: 0084-5930. ISBN: 0-89004-546-1.
DT **Conference**
FS BR; OLD
LA English
CC **General Biology - Symposia, Transactions and Proceedings of Conferences, Congresses, Review Annuals 00520**
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Chemical and Physical *10806
Metabolism - Proteins, Peptides and Amino Acids *13012
Cardiovascular System - Physiology and Biochemistry *14504
BC Suidae 85740
IT Miscellaneous Descriptors
ABSTRACT
RN **9025-75-6** (PHOSPHO PROTEIN PHOSPHATASE)

L150 ANSWER 65 OF 65 BIOSIS COPYRIGHT 2000 BIOSIS
AN 1976:203321 BIOSIS
DN BA62:33321
TI THE EFFECT OF SEVERAL DI PHOSPHONATES ON ACID PHOSPHO HYDROLASES AND OTHER LYSOSOMAL ENZYMES.
AU FELIX R; RUSSELL R G G; FLEISCH H
SO BIOCHIM BIOPHYS ACTA, (1976) 429 (2), 429-438.
CODEN: BBACAQ. ISSN: 0006-3002.
FS BA; OLD
LA Unavailable
AB Diphosphonates inhibit bone resorption in tissue culture and in experimental animals. This effect may be due to their ability to inhibit the dissolution of hydroxyapatite **crystals**, but other mechanisms may be important. Since lysosomal enzymes are implicated in the process of bone resorption, the effect of several phosphonates and a polyphosphate (P20,i) was studied on lysosomal hydrolases derived from rat liver and rat bone. Dichloromethylene diphosphonate strongly inhibited acid .beta.-glycerophosphatase (EC 3.1.3.2) and acid p-nitrophenyl phosphatase (EC 3.1.3.2) and to a lesser degree (in descending order) acid pyrophosphatase (EC 3.1.3.-), arylsulfatase A (EC 3.1.6.1), deoxyribonuclease II(EC 3.1.4.6) and **phosphoprotein phosphatase** (EC 3.1.3.6) of rat liver. Inhibition of acid p-nitrophenyl phosphatase and arylsulfatase A was competitive. Ethane-1-hydroxy-1,1-diphosphonate did not inhibit any of these enzymes, except at high concentrations. Neither dichloromethylene diphosphonate nor ethane-1-hydroxy-1,1-diphosphonate had any effect on .beta.-glucuronidase (EC 3.2.1.31), arylesterase (EC 3.1.1.2) and cathepsin D (EC 3.4.23.5). Of several other phosphonates tested only undec-10-ene-1-hydroxy-1,1-diphosphonic acid inhibited acid p-nitrophenyl phosphatase strongly, the polyphosphate (P20,i) had little effect. Acid p-nitrophenyl phosphatase in rat calvaria extract behaved in the same way as the liver enzyme and was also strongly inhibited by dichloromethylene diphosphonate, but not by ethane-1-hydroxy-1,1-diphosphonate. The inhibition of bone resorption by dichloromethylene diphosphonate might be due in part to a direct effect of

this diphosphonate on lysosomal hydrolases.
CC Cytology and Cytochemistry - Animal 02506
Biochemical Studies - General 10060
Biochemical Studies - Proteins, Peptides and Amino Acids 10064
Biophysics - Molecular Properties and Macromolecules 10506
Enzymes - Physiological Studies *10808
Metabolism - Proteins, Peptides and Amino Acids *13012
Bones, Joints, Fasciae, Connective and Adipose Tissue - Physiology and Biochemistry *18004
Pharmacology - Drug Metabolism; Metabolic Stimulators *22003
Pharmacology - Connective Tissue, Bone and Collagen - Acting Drugs *22012
Tissue Culture, Apparatus, Methods and Media 32500
BC Muridae 86375
IT Miscellaneous Descriptors
RAT DI CHLOROMETHYLENE DI PHOSPHONATE ETHANE 1 HYDROXY-1 1 DI PHOSPHONATE UNDEC-10-ENE 1 HYDROXY-1 1 DI PHOSPHONIC-ACID METAB-DRUGS BONE RESORPTION BETA GLYCERO PHOSPHATASE EC-3.1.3.2 P NITROPHENYL PHOSPHATASE ACID PYRO PHOSPHATASE EC-3.1.3.- ARYL SULFATASE A EC-3.1.6.1 DNASE II EC-3.1.4.6 PHOSPHO PROTEIN PHOSPHATASE EC-3.1.3.16 BETA GLUCURONIDASE EC-3.2.1.31 ARYL ESTERASE EC-3.1.1.2 CATHEPSIN D EC-3.4.23.5 LYSOSOMAL HYDROLASES
RN 74-84-0 (ETHANE)
1605-72-7 (DI CHLOROMETHYLENE)
9001-45-0 (BETA GLUCURONIDASE)
9001-45-0 (EC-3.2.1.31)
9001-77-8 (ACID PHOSPHOHYDROLASES)
9001-77-8 (EC-3.1.3.2)
9013-05-2 (PHOSPHATASE)
9016-17-5 (EC-3.1.6.1)
9016-17-5 (ARYL SULFATASE)
9025-26-7 (CATHEPSIN D)
9025-26-7 (EC-3.4.23.5)
9025-64-3 (EC-3.1.4.6)
9025-64-3 (DNASE II)
9025-75-6 (EC-3.1.3.16)
9027-39-8 (BETA GLYCERO PHOSPHATASE)
9032-73-9 (ARYL ESTERASE)
9032-73-9 (EC-3.1.1.2)
9033-44-7 (PYRO PHOSPHATASE)
9073-68-1 (P NITROPHENYL PHOSPHATASE)
36465-90-4 (DIPHOSPHONATES)
36465-90-4 (DI PHOSPHONIC-ACID)
36465-90-4 (DI PHOSPHONATE)